The role of sentinel node tumor burden in modeling the prognosis of melanoma patients with positive sentinel node biopsy: an Italian melanoma intergroup study \((N = 2,086)\)

Saveria Tropea1,2, Paolo Del Fiore1*, Andrea Maurichi3, Roberto Patuzzo3, Mario Santinami3, Simone Ribero4,5, Pietro Quaglino5, Virginia Caliendo6, Lorenzo Borgognoni7, Serena Sestini7, Giuseppe Giudice8, Eleonora Nacchiero8, Corrado Caracò9, Adriana Cordova10, Nicola Solari11, Dario Piazzalunga12, Francesca Taucer13, Paolo Carcoforo14, Maurizio Lombardo15, Sara Cavallari16, Simone Mocellin1,2 and Italian Melanoma Intergroup (IMI)17

Abstract

Background: The management of melanoma patients with metastatic melanoma in the sentinel nodes (SN) is evolving based on the results of trials questioning the impact of completion lymph node dissection (CLND) and demonstrating the efficacy of new adjuvant treatments. In this landscape, new prognostic tools for fine risk stratification are eagerly sought to optimize the therapeutic path of these patients.

Methods: A retrospective cohort of 2,086 patients treated with CLND after a positive SN biopsy in thirteen Italian Melanoma Centers was reviewed. Overall survival (OS) was the outcome of interest; included independent variables were the following: age, gender, primary melanoma site, Breslow thickness, ulceration, sentinel node tumor burden (SNTB), number of positive SN, non-sentinel lymph nodes (NSN) status. Univariate and multivariate survival analyses were performed using the Cox proportional hazard regression model.

Results: The 3-year, 5-year and 10-year OS rates were 79%, 70% and 54%, respectively. At univariate analysis, all variables, except for primary melanoma body site, were found to be statistically significant prognostic factors. Multivariate Cox regression analysis indicated that older age \((P < 0.0001)\), male gender \((P = 0.04)\), increasing Breslow thickness \((P < 0.0001)\), presence of ulceration \((P = 0.004)\), SNTB size \((P < 0.0001)\) and metastatic NSN \((P < 0.0001)\) were independent negative predictors of OS.

Conclusion: The above results were utilized to build a nomogram in order to ease the practical implementation of our prognostic model, which might improve treatment personalization.
Background

The standard treatment of cutaneous melanoma has been wide excision of the primary tumor combined with sentinel node (SN) biopsy for staging purposes, the SN status being one of the strongest predictors of prognosis [1–3]. For many years, completion lymph node dissection (CLND) has been the standard approach for patients with metastatic SN. However, with publication of the Multicenter selective Lymphadenectomy-2 trial (MSLT2) and the German Dermatologic Cooperative Oncology Group study (DeCOG-SLT) and considering the evolving landscape of adjuvant therapy in melanoma patients, immediate CLND is not recommended in the first course [4–8]. MSLT-2 and DeCOG-STLT showed that CLND increases the rate of regional disease control and provides prognostic information but is not associated with an improved melanoma specific survival [5, 6]. However, these trials, the results of which might lead to abandon the practice of CLND, had some limitations. First, retrospective series produced varied results and were subject to a considerable risk of select bias; next, there were differences in clinic-pathologic features of the patient cohorts between centers; moreover, most patients, enrolled in these studies, had a low-volume nodal tumor burden [5, 7, 9–11]. In the end, international guidelines such as those issued by the National Comprehensive Cancer Network, recommend to discuss with the patient the benefit of CLND mainly based on the risk of harboring additional lymph node metastatic disease. In analogy with breast cancer, the current availability of an effective adjuvant therapy (either targeted therapy or immunotherapy) for patients with SN positive melanoma is further pushing against the use of TB and recommended the assessment of tumor load to be performed by every melanoma Center [17–19].

Methods

Study design

This is a retrospective study based on information from prospectively maintained databases managed by 13 Italian centers belonging to the Italian Melanoma Intergroup (IMI).

This study aimed to test the hypothesis that TB significantly contributes to predict overall survival (OS) in patients with metastatic melanoma in the sentinel node(s) who underwent CLND. The results were used to build a prognostic nomogram of clinical use.

Data regarding a cohort of 2,086 patients were reviewed. We considered the following covariates: age (as a continuous value), gender (male vs female), melanoma body site (head and neck, trunk, limbs), Breslow thickness (as a continuous value), ulceration (absent vs present), number of positive sentinel nodes (as a continuous value), sentinel node TB (0.01 mm-0.4 mm; 0.41 mm-0.96 mm; 0.97 mm-3 mm; 3.1 mm-35 mm), non-sentinel lymph node status (positive vs negative).

The main inclusion criteria for SNB was melanoma with Breslow thickness ≥ 1 or melanoma with thinner tumors with adverse prognostic features such as ulceration, a high mitotic rate or Clark level IV o V. The main inclusion criteria for CLND were positive SNB and lack of clinical or radiological evidence of metastatic disease (all patients were M0).
The pathology protocols to assess primary melanoma features, SN and NSN status were shared by all 13 IMI Centers.

T coefficients obtained from the multivariable model were used to set up a nomogram for practical use.

**Statistical analysis**

OS curve was estimated using the Kaplan Meier method. Univariate and multivariate survival analyses were performed using the Cox proportional hazard regression model.

In order to check for model overfitting we used the bootstrap method (1,000 replications). Briefly, random samples drawn with replacement from the original data set are created with the same size as the original series; the performance index of the model built on the entire cohort is always better than the average of the indices calculated in each replication. The difference between the two is an estimate of the model overfitting (optimism) and the average value of the indices is considered the unbiased estimate of how well the model would perform in future data set. The alpha level of significance was set at 5%.

All analyses were performed using Stata 11.2 SE software (StataCorp LLC, College Station, TX, USA).

**Results**

Patients diagnosed with cutaneous melanoma between 2000 and 2018 were studied.

Patients and tumor characteristics are reported in Table 1. Univariate and multivariate survival analyses are reported in Table 2.

The 3-year, 5-year and 10-year OS rates were 79%, 70% and 54%, respectively (Fig. 1). At univariate analysis, all variables, except for primary melanoma body site, were found to be statistically significantly associated with patient prognosis. Multivariate Cox regression analysis indicated that age (HR = 1.01; 95% CI: 1.01–1.02, \( p < 0.0001 \)), male sex (HR = 1.19; 95% CI: 1.00–1.41, \( p = 0.005 \)), Breslow (HR = 1.06; 95% CI: 1.04–1.08, \( p < 0.0001 \)), NSN metastatic status (HR = 2.06; 95% CI: 1.72–2.50, \( p < 0.0001 \)), ulceration (HR = 1.30; 95% CI: 1.08–1.56, \( p < 0.0001 \)) and the diameter of sentinel node metastasis (HR = 1.04; 95% CI: 1.03–1.06, \( p < 0.0001 \)) were independent negative prognostic factors of OS. Number of positive SN did not result a statistically significant predictor of OS.

Table 1 Patients and tumor characteristic

| Variable             | Median (range) | n   | %  |
|----------------------|----------------|-----|----|
| Age (years)          | 56 (4–90)      |     |    |
| Gender               |                |     |    |
| Male                 | 1203           | 58  |    |
| Female               | 883            | 42  |    |
| Melanoma body site   |                |     |    |
| Head and neck        | 130            | 6   |    |
| Trunk                | 1008           | 48  |    |
| Limbs                | 948            | 46  |    |
| Breslow (mm)         | 3,53 (0.30–40) |     |    |
| Ulceration           |                |     |    |
| Yes                  | 960            | 46  |    |
| Not                  | 1126           | 54  |    |
| SN tumor burden      | 2,59 (0.01–35) |     |    |
| 0.01–0.4 mm          | 577            | 27  |    |
| 0.41–0.96 mm         | 471            | 23  |    |
| 0.97–3 mm            | 586            | 28  |    |
| 3.1–35 mm            | 451            | 22  |    |
| NSN status           |                |     |    |
| Positive             | 453            | 22  |    |
| Negative             | 1633           | 78  |    |

As regards TB, we grouped SN metastasis diameter in quartiles and so we identified 4 subgroups of patients (Fig. 2). We found that SN TB was an important predictor of OS with a progressive worsening prognosis from first (0.01 mm–0.04 mm) to fourth subgroup (3.1 mm–35 mm). In details, the latest subgroup had a significantly poor prognosis compared to the other subgroups (HR = 3.51; 95% CI: 2.74–4.49, \( p > 0.0001 \)) (Table 2). A nomogram for clinical and research purposes was built using the coefficients by the multivariate model (Fig. 3).

**Discussion**

We presented the results of a multicentric study aimed at building a prognostic model in melanoma patients with metastatic melanoma in the sentinel node by combining the information of six clinico-pathological variables including tumor burden (TB). Our findings show that TB significantly contributes to predict the prognosis of these patients.

To the best of our knowledge this is the largest series ever published with this aim, as previous studies have addressed the same issue using data from smaller series of patients. The negative prognostic value of TB, as maximum SN tumor size > 1 mm, was already assessed in terms of non-sentinel node positivity, disease free survival and melanoma specific survival by an international multicentric study of 1,539 SN positive melanoma patients [1].

Another study analyzing 104 SN positive patients who underwent CLND demonstrated that the 5-year melanoma specific survival for CLND-negative patients was 5 years as compared to 3.69 years in CLND positive patients. In this analysis, clinico-pathological parameters such as diameter of tumor deposit, distribution of
metastatic focus within the sentinel node, ulceration and number of metastatic melanoma in the sentinel nodes were evaluated and the investigators found that TB > 4 mm and multifocal metastatic disease within the sentinel node were the most important variables that allowed an accurate prognostic stratification of patients [11].

On behalf of the EORTC-DeCOG, some authors developed prediction models for disease recurrence, distant metastasis (DM) and overall mortality analyzing a retrospective cohort of 1,080 patients. The resulting EORTC-DeCOG nomogram included parameters as ulceration, age, sentinel node TB, and Breslow: therefore, this study included only information deriving from the primary melanoma and the SNB, without considering the status of non-sentinel nodes [5].

In 2019, Satzger et al., assessing a total of 736 positive SN melanoma patients, demonstrated that TB, Breslow, ulceration and age are independent prognostic factors of melanoma specific survival. In detail, MSS was significantly better in patients with lower SN TB than in patients with higher SN TB (> 0.5 mm and > 1 mm) [17].

Overall, our results are consistent with the previous studies and confirm the prognostic value of TB. Our findings, along with the already existing literature on this subject, support the hypothesis that prognosis decays continuously with increasing maximum diameter of the larger metastatic deposit within the sentinel node: therefore, accumulating evidence strongly suggest that TB represents an important piece of information while stratifying the risk of these patients, even if the ideal cut-off needs to be determined.

In our opinion, CLND adds prognostic information as the status of non-sentinel nodes is an independent prognostic feature, as we have demonstrated not only in the present analysis but also previously [6, 11]. Therefore, CLND not only improves regional relapse-free survival (as demonstrated by the results of the MSLT-II) but also provides physicians with useful prognostic information [6–8].

### Table 2 Results of univariate and multivariate analysis

| Variable                      | N   | 5-YSR (%) | 10-YSR (%) | UNIVARIATE HR | P-value | MULTIVARIATE HR | P-value |
|-------------------------------|-----|-----------|------------|---------------|---------|----------------|---------|
| Age                           |     |           |            | 1.02 (1.02–1.03) | <0.0001 | 1.01 (1.01–1.02) | 0.0001  |
| Gender                        |     |           |            | Reference     |         | Reference       |         |
| Female                        | 883 | 74        | 60         | 1.33 (1.12–1.58) | 0.0005 | 1.19 (1.00–1.41) | 0.04    |
| Male                          | 1203| 63        | 50         | 0.58          |         |                 |         |
| Melanoma body site            |     |           |            | Reference     |         | Reference       |         |
| Breslow                       |     |           |            | Reference     |         | Reference       |         |
| Ulceration                    |     |           |            | Reference     |         | Reference       |         |
| Not                           | 1126| 76        | 63         | 1.86 (1.57–2.20) | <0.0001 | 1.30 (1.08–1.56) | 0.004   |
| Yes                           | 960 | 60        | 42         | 1.22 (1.06–1.41) | 0.0066 |                 | 0.16    |
| Number of positive SN         |     |           |            | Reference     |         | Reference       |         |
| SN tumor burden               |     |           |            | Reference     |         | Reference       |         |
| 0.01–0.4 mm                   | 577 | 82        | 68         | 1.27 (1.01–1.59) | <0.0001 |                 |         |
| 0.42–0.96 mm                  | 471 | 76        | 58         | 1.89 (1.54–2.34) | <0.0001 |                 |         |
| 0.97–3 mm                     | 586 | 66        | 52         | 3.51 (2.74–4.49) | <0.0001 |                 |         |
| 3.1–35 mm                     | 452 | 49        | 34         |             |         |                 |         |
| NSN Status                    |     |           |            | Reference     |         | Reference       |         |
| Negative                      | 1633| 75        | 61         | 2.06 (1.72–2.5) | <0.0001 |                 |         |
| Positive                      | 453 | 46        | 31         |               |         |                 |         |

![OS Kaplan Meier curve](image)
For practical purposes, we generated a nomogram to easily personalize the prediction of patient prognosis. More precise risk stratification is important for adequate patient information on the severity of the disease and is especially useful for selecting patients who can benefit most from adjuvant therapy. Moreover, our nomogram could enable physicians to personalize the intensity of patients follow up as well as to optimize patient allocation within the frame of clinical trials.

Finally, we recognize that the present study has some limitations. First, it is a retrospective multicentric study with inherent bias: however the analyses were performed on complete cases without missing data. Second, we could not validate our results in an external series of
patients, which would improve the assessment of model generalizability. Third, a good proportion of patients received interferon-alpha based adjuvant therapy, which could have potentially influenced the outcome, especially in patients with ulcerated melanoma. Moreover, some patients were treated with modern treatments (e.g., targeted therapy or immunotherapy) after disease recurrence, which could also have affected overall survival. We could not explore the impact of adjuvant therapy on OS because of insufficient data.

In addition, other potential prognostic factor as mitotic rate could not be incorporated in our analysis due to lack of complete data.

As regards the future perspective of survival predictive models, we believe that only the implementation of informative biomarkers will help improve the accuracy of current prognostic tools. Investigation on the molecular mechanisms underlying melanoma progression and aggressiveness has led to the identification of hundreds of potential such biomarkers [4–7, 18]; unfortunately, none of them has been so far associated with a predictive value independent of conventional clinico-pathological parameters. Therefore, more work is eagerly needed to make further advances in this field of investigation.

Acknowledgements

We would like to express our special thanks to Prof. Carlo Riccardo Rossi for his long-term contribution to the study and for his ideas and support of this current manuscript. The authors would like to thank the Intergruppo Melanoma Italiano (IMI)1-34 and his present chairman Prof Ignazio Stanganelli.

INTERGRUPPO MELANOMA ITALIANO (IMI)1-34

Maddalena Cespa1, Fondazione IRCCS Policlinico San Matteo Clinica Dermatologica, Pavia;

Rossiachia Forcignano2, Azienda Ospedaliera Vito Fazzi, U.O. Di Oncologia, Lecco;

Gianmichele Mosiè1, Azienda Per I Servizi Sanitari N.2 Isontina Ospedale Di Gorizia Dipartimento Di Medicina, S.O.S. Di Dermatologia – Gorizia;

Maria Concetta Fargnoli3, Presidio Ospedaliero San Salvatore, U.O.S. Di Dermatologia Generale Ed Oncologia, L’Aquila;

Caterina Ferrelli4, Università Degli Studi Di Cagliari -Azienda Ospedaliero Universitaria, Clinica Dermatologica, Cagliari;

Maria Grimaldi5, Istituto Nazionale dei Tumori Fondazione G. Pascale Napoli;

Guido Zannetti6, Azienda Ospedaliero-Universitaria Di Bologna Policlinico S. Orsola –Malpighi, Chirurgia Plastica, Bologna;

Saverio Cinieri7, Presidio Ospedaliero Antonio Perrino, U.O.C. Di Oncologia E Breast Unit, Brindisi;

Giusto Trevisan8, Ospedale Maggiore, Azienda Ospedaliera Universitaria Di Trieste, Clinica Dermatologica, 4° Piano (Palazzina Infettiva), Trieste;

Ignazio Stanganelli9, Ospedale S. Maria Delle Croci—Usl Di Ravenna, Centro Di Dermatologia Oncologica CPO/IRST, Ravenna;

Giovanna Moretti10, Azienda Ospedaliera Ospedali Riuniti Papardo-Piemonte S.C. Dermatologia Messina;

Francesca Bruder11, Ospedale Oncologico, Dipartimento Melanoma E Tumori Rari 5° Piano, Cagliari;

Luca Bianchi12, Azienda Ospedaliera Universitaria Policlinico Tor Vergata U.O.C. Dermatologia Roma;

Maria Teresa Fierro13, A.O.U. Città Della Salute E Della Scienza—P.O. San Lazaro, S.C. Dermatologia Forno, Luiggi Mascheroni14, Humanitas—Casa Di Cura San Pio X S.R.L, Chirurgia Generale Milano;

Salvatore Asero15, Azienda Ospedaliera Di Rilevio Nazionale E Di Altra Specializzazione Garibaldi-Nesima, U.O. Di Chirurgia Oncologica—Dip. Oncologia, Catania;

Caterina Catricala16, Istituto Dermatologico San Gallicano IRCCS—FIU, U.O. di Dermatologia Oncologica—Dipartimento Clinico-Sperimentale Di Dermatologia Oncologica Roma;

Stefania Scalabino16, Azienda Ospedaliera Universitaria Federico II di Napoli, Scienze Biomorfologiche e Funzionali- Sezione DI Anatoomia Patologica, Napoli;

Gaetana Rinaldi17, Azienda Ospedaliera Universitaria Policlinico ‘Paolo Giaccone’, Dipartimento Di Oncologia—U.O. Oncologia Medica, Palermo;

Riccardo Pelliccioni18, IRCCS Casa Sollievo Della Sofferenza, U.O.C. Dermatologia, San Giovanni Rotondo;

Laura Mileri19, Azienda Ospedaliera Papa Giovanni XXIII, USC Oncologia Medica, Bergamo;

Marilena Visini20, A.O. Di Lecco Presidio Ospedaliero Alessandro Manzoni, Oncologia Medica, Lecco;

Franco Di Filippo21, Istituto Nazionale Tumori Regina Elena IRCCS – IFO, Chirurgia Generale A, Roma;

Leonardo Zichichi22, Azienda Sanitaria Provinciale—Presidio Ospedaliero Di Trapani, U.O. C. Dermatologia, Casa Santa – Erice;

Maria Antonietta Pizzichetta23, Centro Di Riferimento Oncologico, IstitutoNazionale Tumori, Divisione Di Oncologia Medica C, Aviano;

Carmelo Iacono26, Azienda Ospedaliera Sanitaria 7 Ragusa—Ospedale Maria Paterño Areezo, Dipartimento Di Oncologia, Ragusa;

Massimo Guidoboni27, I.R.S.T. Istituto Scientifico Romagnolo Per Lo Studio E La Cur Di Tumori U.O. Immunoterapia E Terapia Cellulare Somatica, Melelda;

Giovanni Sarona28, Azienda Ospedaliero-Universitaria Di Sassari, Servizio Di Medicina Nucleare U.O. Di Oncologia Medica, Sassari;

Michele Maio29, Azienda Ospedaliera Universitaria Senese Ospedale Le Scotte U.O.C. Immunoterapia Oncologica, Siena;

Michele Del Vecchio30, Fondazione I.R.C.C.S. Istituto Nazionale Dei Tumori, S.C. Medicina Oncologica 1, Milano;

Lucia Lospalluti31, Azienda Sanitaria Locale BA—Ospedale Di Venere, U.O. Dermatologia, Carbonara Di Bari, Rosanna Barbati, Asl Roma C—Ospedale S. Eugenio, U.O. Dermatologia, Roma;

Leonardi Vita32, ARNAS Civico Palermo, Annamaria Pollio33, Ospedale “A. Cardarelli” – Campobasso, U.O.C. Di Anatomia Patologica;

Carlo Riberti34, Istituto di Chirurgia Plastica presso l’Arcispedale Sant’Anna, Ferrara.

Authors’ contributions

Study concepts: SM, ST. Study design: SM, ST. Data acquisition: AM, RP, NS, SB, PQ, VC, LB, SS, GG, EN, CC, AC, NS, DF, FT, PC, ML, SC. Quality control of data and algorithms: SM, ST, PDF. Data analysis and interpretation: SM, ST. Statistical analysis: SM, ST. Manuscript preparation: SM, ST. Manuscript editing: ST, PDF. Manuscript review: SM, ST. All authors contributed to the article and approved the submitted version.

Funding

This research received funds from ‘Ricerca Corrente 2022’ to cover publication costs.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to ensuring the confidentiality and anonymity of the participants but are available from paolo.delfiore@iov.veneto.it on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Veneto Institute of Oncology (CESC-IOV) on 03 February 2015. All methods were performed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study in accordance with the relevant guidelines and regulations of CESC-IOV.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Author details
1 Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, 35128 Padua, Italy. 2 Department of Surgery, Oncology and Gastroenterology (DISCGO), University of Padua, Padua, Italy. 3 Fondazione IRCCS Istituto Nazionale Dei Tumori, Melanoma and Sarcoma Unit, Milan, Italy. 4 Department of Dermatologic Surgery, Città della Salute e della Scienza, Turin, Italy. 5 Department of Medical Sciences, Clinic of Dermatology, University of Turin, Turin, Italy. 6 Dermatologic Surgery Section, Oncologic Department, “Città della Salute E Della Scienza Di Torino” University Hospital, Turin, Italy. 7 SOC Chirurgia Plastica Ristrutturativa E Melanoma & Skin Cancer Unit, Osp. SM Annunziata, AUSL Toscana Centro, Florence, Italy. 8 U.O.C. Di Chirurgia Plastica Ricostruttiva E Centro Ustioni Policlinico, University of Bari, Bari, Italy. 9 Corrado Caracò M.D., Struttura Complessa Chirurgia Oncologica e Melanoma - Istituto Nazionale Tumori-Fondazione “G. Pascale”, Naples, Italy. 10 Department of Surgical Oncologic and Stomatologic Sciences, University of Palermo, Palermo, Italy. 11 Chirurgia Ospedaliera 1 Ospedale Policlinico San Martino, Genoa, Italy. 12 Chirurgia Generale 1, Ospedale Papa Giovanni XXIII, Bergamo, Italy. 13 Chirurgia E Terapie Oncologiche Avanzate Ospedale “GB. Morgagni-L. Piorantoni” - AUSL Forlì, Forlì, Italy. 14 UOC Chirurgia II Azienda Ospedaliera Universitaria Di Ferrara, Ferrara, Italy. 15 Dermatology Unit, Department of Specialistic Medicine, ASST Dei Sette Laghi, Varese, Italy. 16 M.D.S. C. Chirurgia Generale ASST Carlo Poma, Mantua, Italy. 17 Italian Melanoma Intergroup (IMI), 16121 Genoa, Italy.

Received: 7 October 2021   Accepted: 26 May 2022

Published online: 03 June 2022

References
1. van der Ploeg AP, van Akkooi AC, Haydu LE, et al. The prognostic significance of sentinel node tumour burden in melanoma patients: an international, multicenter study of 1539 sentinel node-positive melanoma patients. Eur J Cancer. 2014;50(1):111–20.
2. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992;127(4):392–9.
3. Namikawa K, Aung PP, Milton DR, et al. Crelaration of tumor burden in sentinel lymph nodes with tumor burden in non-sentinel lymph nodes and survival in Cutaneous Melanoma. Clin Cancer Res. 2019;25(24):7585–93.
4. Rossi CR, Mocellin S, Campana LG, Italian Melanoma Intergroup (IMI), et al Prediction of non-sentinel node status in patients with melanoma and positive sentinel node biopsy: an Italian Melanoma Intergroup (IMI) study. Ann Surg Oncol. 2018;25(1):271–9.
5. Verder, R, Rekkas A, Garbe C, et al. The EORTC-DeCOG nomogram adequately predicts outcomes of patients with sentinel node-positive melanoma without the need for completion lymph node dissection. Eur J Cancer. 2020;1349–18.
6. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in Melanoma. N Engl J Med. 2017;376(23):2211–22.
7. Verder, D, van Klaveren D, van Akkooi AC, et al. Risk stratification of sentinel node-positive melanoma patients defines surgical and adjuvant therapy treatment considerations. Eur J Cancer. 2018;96:25–33.
8. Leiter U, Stadler R, Mauch C, German Dermatologic Cooperative Oncology Group (DeCOG), et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2016;17(6):757–67.
9. Leiter U, Stadler R, Mauch C, German Dermatologic Cooperative Oncology Group, et al. Final analysis of DeCOG-SLT trial: no survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. J Clin Oncol. 2019;37(32):3000–8.
10. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. Gershenwald JE, Scolyer RA, Hess KR, et al. for members of the American Joint Committee on Cancer Melanoma Expert Panel and the International Melanoma Database and Discovery Platform. Gershenwald JE, et al. CA Cancer J Clin. 2017;67(6):472–492.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.