INVASIVE CUTANEOUS MELANOMA: SURVIVAL AND PROGNOSTIC FACTORS

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RESUMO: O melanoma cutâneo invasivo é uma neoplasia maligna de características heterogêneas, com potencial comportamento biológico agressivo. Com o objetivo de estimar a sobrevida global doença-específica em indivíduos acometidos por melanoma cutâneo invasivo e analisar sua relação com fatores de risco, foi realizado um estudo de coorte com 221 participantes tratados em um serviço de oncologia no período de 2000 a 2023. O seguimento mediano da coorte foi superior a 13 anos. A sobrevida global doença-específica foi estimada pelo método de Kaplan-Meier, e a análise da associação entre as variáveis prognósticas foi realizada por meio do modelo de riscos proporcionais de Cox. A idade mediana dos participantes foi de 54 anos. As taxas estimadas de sobrevida global doença-específica foram de 96,8% no primeiro ano, 94,9% aos 2 anos, 90,4% aos 5 anos e 87,0% aos 10 anos. A análise das variáveis clínicas indicou que os níveis de Clark IV e V, o índice de Breslow acima de 2,6 mm, a presença de ulceração, a ausência ou infiltração linfocitária leve, o número de mitoses acima de 5/mm² e os estágios III e IV (TNM) foram identificados como marcadores independentes de pior prognóstico. Conclui-se que a classificação de Clark, o índice de Breslow, a presença de ulceração na lesão primária, o grau de infiltração linfocitária, a taxa de mitoses e o estágio clínico são importantes fatores preditivos de risco em indivíduos com melanoma cutâneo invasivo.

Palavras-chave: Melanoma. Sobrevida. Epidemiologia.

ABSTRACT: Cutaneous invasive melanoma is a malignant neoplasm characterized by heterogeneity and the potential for aggressive biological behavior. To estimate disease-specific survival in individuals diagnosed with cutaneous invasive melanoma and to analyze its association with risk factors, a cohort study was conducted involving 221 participants treated at an oncology center between 2000 and 2023. The median follow-up duration exceeded 13 years. Disease-specific survival was estimated using the Kaplan-Meier method, and associations with prognostic variables were analyzed using the Cox proportional hazards model. The median age of participants was 54 years. Estimated disease-specific survival rates were 96.8% at 1 year, 94.9% at 2 years, 90.4% at 5 years, and 87.0% at 10 years. The analysis identified several clinical variables as independent markers of poor prognosis: Clark levels IV and V, Breslow index greater than 2.6 mm, presence of ulceration, absent or mild lymphocytic infiltration, mitotic rate exceeding 5/mm², and TNM stages III and IV. In conclusion, Clark level, Breslow index, presence of ulceration in the primary lesion, degree of lymphocytic infiltration, mitotic rate, and clinical stage are important predictive risk factors in individuals with invasive cutaneous melanoma.

Keywords: Melanoma. Survival. Epidemiology.

INTRODUCTION

Cutaneous melanoma (CM) is the most aggressive form of invasive malignant neoplasm of the skin, despite being the least frequent type of skin cancer. It accounts for approximately 1% of skin cancer cases in the United States and 3% in Brazil (1–3). Originating from melanocytes, CM is characterized by a heterogeneous oncological behavior, typically associated with a favorable prognosis when diagnosed at early stages, but potentially highly aggressive if identified in advanced stages (1,3).

In Brazil, an estimated 704,000 new cancer cases are expected annually during the 2023–2025 triennium, with the highest incidence observed in the South and Southeast regions, which together account for approximately 70% of cases (2). Regarding melanoma specifically, 325,000 new cases were estimated in 2020, representing approximately 1.7% of all skin cancers. Of these, 175,000 were diagnosed in men (3.80 per 100,000) and 151,000 in women (3.00 per 100,000). The South region of Brazil shows a higher prevalence of melanoma in both sexes compared to other regions of the country (2).

In the United States, 97,620 new cases of invasive melanoma and 89,070 cases of melanoma *in situ* were projected for 2023, with 7,990 deaths attributed to the disease (1). In Europe, the annual incidence of malignant melanoma ranges from 3 to 5 per 100,000 in Mediterranean countries to 12 to 35 per 100,000 in Nordic countries. In countries such as Australia and New Zealand, incidence rates may exceed 50 per 100,000. Globally, the incidence of melanoma has been increasing steadily over the past four decades, although mortality appears to be stabilizing—except among elderly men (4).

According to the International Agency for Research on Cancer, there were an estimated 324,635 new cases and 57,043 deaths due to melanoma worldwide in 2020 (5).

There is a scarcity of regional epidemiological studies in Brazil that specifically address melanoma survival rates and investigate prognostic factors associated with the disease (6). In this context, the present cohort study was conducted in the northern region of Rio Grande do Sul with the objective of evaluating survival rates in cases of invasive cutaneous melanoma and examining their association with clinical and histopathological risk factors in the affected population.

METHOD

This retrospective cohort study was based on hospital records of individuals diagnosed with invasive cutaneous melanoma who received cancer treatment at the Clinical Oncology and Radiotherapy Center in Erechim, Rio Grande do Sul, between 2000 and 2023. Inclusion criteria comprised a confirmed diagnosis of invasive cutaneous melanoma by histopathological examination and having undergone oncological treatment at any time during the designated study period. Data on initial exposure (histopathological diagnosis), clinical characteristics, and outcomes (censoring or death) were collected through a systematic review of hospital medical records. The study was conducted in accordance with the ethical principles outlined in Resolution No. 466/12 of the National Health Council of the Ministry of Health (CNS/MS) and was approved by the Research Ethics Committee (CEP) of the Integrated Regional University (URI) of Erechim-RS, under approval number 6.136.573, dated June 22, 2023.

For the survival analysis, the following criteria were applied: the observation period commenced on the date of the histopathological diagnosis; the final day of 2023 was established as the cut-off date for cohort entry; and follow-up extended until March 30, 2024. Death due to melanoma or directly related to its treatment was considered the primary outcome for the analysis of overall survival. Deaths from other causes were treated as censored events, with censoring occurring on the date of death. Participants who remained alive at the end of the follow-up period were censored at the date of the last entry in their medical records. Those lost to follow-up contributed to the survival analysis until the last recorded date in their medical records.

The risk factors (explanatory variables) considered in the analysis included: age, sex, histological subtype, primary tumor location, Clark level, Breslow thickness, presence of ulceration, degree of lymphocytic infiltration, mitotic index, and clinical stage (TNM classification) of the primary tumor.

These variables were stratified based on cut-off points established in the literature and were presented both descriptively and analytically. The survival function was estimated using the Kaplan-Meier method. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated to assess the

association between prognostic variables and the risk of death, using Cox proportional hazards models to determine statistical significance.

RESULTS

Table 1 presents the characteristics of the study cohort and the association between the selected variables and the occurrence of death as an outcome. The mean follow-up duration for the cohort of 221 participants was 13.3 years. Data for the variables of interest were complete, with the exception of lymphocytic infiltration in tumor tissue, which was available for 200 participants (90.5%), and the mitotic index (number of mitoses/mm²), which was documented for 191 participants (86.4%) within the cohort.

The median age of the cohort was 54 years, with a minimum age of 19 and a maximum of 89 years. A predominance of participants (45.7%) were aged between 40 and 59 years. Among the 221 individuals included in the study, 113 (51.1%) were female and 108 (48.9%) were male.

Regarding histological subtype, superficial spreading melanoma was the most prevalent, observed in 134 participants (60.6%). The nodular subtype was identified in 63 participants (28.5%), while other histological variants were found in 24 participants (10.9%).

The primary anatomical site of the melanoma was the head and neck region in 46 participants (20.8%), the trunk in 98 participants (44.3%), and the limbs or other locations in 77 participants (34.9%).

Clark's histopathological levels were stratified as follows: levels I to III were observed in 133 participants (60.2%), level IV in 69 participants (31.2%), and level V in 19 participants (8.6%). In relation to Breslow thickness, 95 participants (43%) presented with a tumor thickness of <0.75 mm; 59 participants (26.7%) with a thickness between 0.75–1.50 mm; 20 participants (9%) between 1.51–2.25 mm; 16 participants (7.3%) between 2.26–3.00 mm; and 31 participants (14%) with a thickness >3.00 mm.

Ulceration of the primary tumor was assessed, with 149 participants (67.4%) presenting without ulceration and 72 participants (32.6%) exhibiting ulceration. Regarding lymphocytic infiltration, 104 participants (52%) demonstrated absent or mild

infiltration, 74 participants (37%) had moderate infiltration, and 22 participants (11%) showed intense lymphocytic infiltration.

The mitotic rate of the primary tumor, measured in mitoses per mm², was also evaluated. Among the cohort, 102 participants (53.4%) had no detectable mitoses; 57 participants (29.8%) exhibited 1 to 4 mitoses/mm²; 14 participants (7.4%) had 5 to 7 mitoses/mm²; and 18 participants (9.4%) demonstrated more than 8 mitoses/mm².

Clinical staging at the time of diagnosis, based on the TNM classification, revealed that 132 participants (59.7%) were in Stage I; 44 participants (19.9%) in Stage II; 29 participants (13.1%) in Stage III; and 16 participants (7.3%) in Stage IV.

At the conclusion of the follow-up period, 194 participants (87.8%) were alive, while 27 participants (12.2%) had died due to invasive cutaneous melanoma. The median disease-specific survival rate was estimated at 96.8% at 1 year, 94.9% at 2 years, 90.4% at 5 years, and 87.0% at 10 years of follow-up (Figure 1).

DISCUSSION

The analysis of prognostic factors within the studied cohort revealed certain predictive associations. Age was not statistically significant in relation to prognosis across the intervals analyzed; however, there was a trend toward increased mortality among participants aged 60 years or older (Hazard Ratio [HR] = 8.02; 95% Confidence Interval [CI]: 1.04–61.34; p = 0.045). In Europe, the incidence of melanoma peaks at approximately 65 years of age, although individuals of all ages may be affected (4).

As for gender, no statistically significant association with prognosis was observed. Nevertheless, there were 17 deaths (15.7%) among male participants, suggesting a trend toward poorer outcomes in this group (HR = 1.86; 95% CI: 0.85–4.07; p = 0.118). A cohort study conducted in São Paulo in 2020 reported lower survival rates among male patients with invasive cutaneous melanoma (7). Similarly, a study published in 2021 also identified a worse prognosis for invasive melanoma in men (8).

The histological subtypes of cutaneous melanoma were categorized into three groups for analysis. Among these, the nodular subtype was associated with a significantly poorer prognosis when compared to the superficial spreading subtype. Participants with nodular melanoma exhibited a higher risk of mortality (14 death events; Hazard Ratio [HR] = 2.25; 95% Confidence Interval [CI]: 1.06–4.78; p = 0.035). In contrast, a cohort study conducted in São Paulo did not identify a statistically

significant difference in survival based on histological subtype (7). A possible explanation for this discrepancy is that nodular melanomas tend to present with greater thickness, which may independently contribute to poorer outcomes (9).

The distribution of the primary anatomical location of the tumor was also assessed. The trunk was the most frequently affected region (44.3%), followed by the lower limbs (34.9%) and the head and neck region (20.8%). However, no statistically significant association was found between tumor location and prognosis. A Japanese study published in 2018 reported that the sole of the foot was the most common site of melanoma in both sexes, with a higher prevalence of lower limb involvement in women (9).

Clark's classification, which evaluates the level of tumor invasion, revealed that cases classified as Clark levels IV and V were significantly associated with worse prognosis when compared to levels I–III. Specifically, Clark level IV was associated with an HR of 44.96 (95% CI: 6.01–336.26; $p < 0.001$), and Clark level V with an HR of 54.60 (95% CI: 6.71–443.86; $p < 0.001$). In contrast, the 18-year retrospective study from São Paulo published in 2021, while reporting a predominance of Clark level IV, did not observe statistically significant prognostic differences across Clark levels (8).

Breslow thickness is a well-established prognostic indicator for invasive melanoma (10). In our cohort study, a clear trend was observed indicating that increased tumor thickness is associated with a poorer prognosis. Notably, tumors with a Breslow thickness greater than 2.26 mm were statistically associated with the worst outcomes when compared to those with a thickness less than 0.75 mm. Similarly, a cohort study conducted in São Paulo and published in 2020 reported that the risk of mortality was 5.37 times higher in cases with a Breslow thickness exceeding 4.0 mm compared to those with a thickness below 0.75 mm (7).

Ulceration was identified in 32.6% of the cases in our cohort. Statistical analysis revealed that the presence of ulceration in the primary tumor increased the risk of death by a factor of 10.23 compared to non-ulcerated cases. A 2004 study, which contributed to the validation of ulceration as a prognostic factor in the American Joint Committee on Cancer (AJCC) staging system for melanoma, similarly demonstrated lower survival rates among patients with ulcerated tumors measuring between 2 and 4 mm in thickness. However, this association did not reach statistical significance in tumors with

a thickness of less than 1 mm or greater than 4 mm, as assessed using the Cox proportional hazards model (11).

It is important to note that the data used to construct the cohort were obtained through the analysis of histopathological reports, which, at present, must adhere to the criteria established in the eighth edition of the American Joint Committee on Cancer (AJCC) melanoma staging and metastasis classification (TNM). These reports include critical parameters such as the maximum tumor thickness in millimeters (Breslow), reported to the nearest 0.1 mm (rounded from 0.05 mm), the presence of ulceration, and the status of surgical margins. Although mitotic rate and the presence of regression are not formally included in the eighth edition of the AJCC classification, their evaluation is recommended across all tumor thickness categories due to their significant prognostic relevance (4, 12).

In the present cohort, lymphocytic infiltration and mitotic rate per mm^2 were also assessed. Data on lymphocytic infiltration were available for 90.4% of cases. Absence or minimal lymphocytic infiltration was associated with a poorer prognosis, with 22.7% of deaths occurring in this subgroup (HR = 9.21; 95% CI: 2.20–38.53; $P < 0.002$). A previous study evaluating the association between lymphocytic infiltration and sentinel lymph node metastasis, conducted between 2003 and 2015, found that moderate lymphocytic infiltration served as a protective predictive factor against sentinel lymph node involvement in invasive melanomas (13).

Mitotic rate per mm^2, available in 86.4% of cases, also demonstrated a statistically significant association with poorer outcomes. The subgroups with mitotic rates of 5–7 mitoses/mm^2 and ≥8 mitoses/mm^2 exhibited the worst prognoses when compared to cases with no detectable mitotic activity. While the mitotic rate holds independent prognostic value in the evaluation of invasive melanoma, its predictive impact is generally considered to be less significant than that of primary tumor thickness and the presence of ulceration (14).

Over the past decade, more than a dozen new therapeutic agents have been approved for the treatment of unresectable melanoma, alongside several new approvals in the adjuvant setting and a growing body of research exploring neoadjuvant strategies. These advancements have contributed to a marked improvement in overall survival rates, with significant increases in long-term survival observed following the introduction of these novel therapies. However, the expansion

of therapeutic options and the corresponding increase in survival have also resulted in longer consultation times and increased financial burdens for both patients and healthcare systems (15).

In this evolving therapeutic landscape, accurate staging using the AJCC classification system remains essential for guiding optimal treatment planning (4, 12, 16). In the present cohort, staging was performed according to the TNM system, and the following five-year survival estimates were observed, as illustrated by the Kaplan-Meier survival curves: Stage I, 100%; Stage II, 95.2%; Stage III, 77.5%; and Stage IV, 25% (Figure 2). Stages III and IV were associated with significantly worse prognoses when compared to Stage I, with eight deaths recorded in Stage III and fifteen deaths in Stage IV over the extended follow-up period.

It is important to highlight that, in this retrospective cohort, no patients were documented to have received adjuvant or neoadjuvant therapies.

CONCLUSIONS

In this study, we observed findings consistent with those reported in the literature. With a long-term follow-up of the cohort, the estimated overall disease-specific survival was 90.4% at five years and 87% at ten years, irrespective of individual prognostic variables. Among the variables analyzed, Clark's level, Breslow thickness, presence of ulceration in the primary lesion, degree of lymphocytic infiltration, mitotic rate, and clinical stage were identified as significant prognostic factors for patients with invasive cutaneous melanoma.

Regional cohort studies play a critical role in elucidating the epidemiological characteristics of specific populations and are essential for informing the planning and optimization of oncology care within local healthcare systems. In this context, the findings of the present study enhance our understanding of the natural history of cutaneous melanoma and support the development of more effective strategies for screening and early diagnosis. This, in turn, contributes to a more efficient and rational allocation of healthcare resources.

REFERENCES

[1] Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA: A Cancer J Clin 2023;73:17–48. https://doi.org/10.3322/caac.21763.
[2] BRASIL. Instituto Nacional de Câncer (Brasil). Estimativa 2023: incidência de câncer no Brasil / Instituto Nacional de Câncer. – Rio de Janeiro: INCA, 2022. https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2023.pdf

[3] Leonardi G, Falzone L, Salemi R, et al. Cutaneous melanoma: From pathogenesis to therapy (Review). Int J Oncol 2018;52. https://doi.org/10.3892/ijo.2018.4287.

[4] Michielin O, van Akkooi ACJ, Ascierto P, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30. https://doi.org/10.1093/annonc/mdz411.

[5] Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview. Int J Caner 2021;149:778–89. https://doi.org/10.1002/ijc.33588.

[6] Moreno M, Batista FRB, Bonetti TC. Sobrevida de Pacientes com Melanoma Cutâneo na Região Oeste de Santa Catarina, Brasil. Ver Bras Cancerol 2012;58:647–53. https://doi.org/10.32635/2176-9745.rbc.2012v58n4.567.

[7] Giavina-Bianchi MH, Festa-Neto C, Sanches JA, et al. Pior sobrevida do melanoma invasivo em homens e em lesões “de novo.” An Bras Dermatol 2020;95:158–64. https://doi.org/10.1016/j.abdp.2019.07.003.

[8] Souza BC, Silva DHM, Valente NYS, et al. Cutaneous melanoma: a retrospective study of 18 years. Are there gender differences? An Bras Dermatol 2021;96:619–23. https://doi.org/10.1016/j.abd.2020.08.022.

[9] Ishihara K, Saida T, Otsuka F, et al. Statistical profiles of malignant melanoma and other skin cancers in Japan: 2007 update. Int. J. Clin. Oncol 2008;13:33–41. https://doi.org/10.1007/s10147-007-0751-1.

[10] Balch CM, Gershenwald JE, Soong S, et al. Final Version of 2009 AJCC Melanoma Staging and Classification. J. Clin. Oncol 2009;27:6199–206. https://doi.org/10.1200/jco.2009.23.4799.

[11] Eigentler TK, Buettner PG, Leiter U, et al. Impact of Ulceration in Stages I to III Cutaneous Melanoma As Staged by the American Joint Committee on Cancer Staging System: An Analysis of the German Central Malignant Melanoma Registry. J. Clin. Oncol 2004;22:4376–83. https://doi.org/10.1200/jco.2004.03.075.

[12] Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J. Clin 2017;67:472–92. https://doi.org/10.3322/caac.21409.

[13] Santos FDM, Silva FC, Pedron J, et al. Association between tumor-infiltrating lymphocytes and sentinel lymph node positivity in thin melanoma. An Bras Dermatol 2019;94:47–51. https://doi.org/10.1590/abd1806-4841.20197414.

[14] Francken AB, Shaw HM, Thompson JF, et al. The Prognostic Importance of Tumor Mitotic Rate Confirmed in 1317 Patients With Primary Cutaneous Melanoma and Long Follow-Up. Ann Surg Oncol 2004;11:426–33. https://doi.org/10.1245/aso.2004.07.014.

[15] Seth R, Agarwala SS, Messersmith H, et al. Systemic Therapy for Melanoma: ASCO Guideline Update. J Clin Oncol 2023;41:4794–820. https://doi.org/10.1200/jco.23.01136.

[16] Amin MB, Edge SB, Greene FL, et al. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017

Table 1: Association between selected factors and the occurrence of death in a cohort of 221 patients with melanoma, Erechim, RS.

			death			
Variables	**n**	**%**	**events**	**%**	***HR* (IC95%)**	**P**
Age						
<40	42	19	1	2.4	1	
40 – 59	100	45.2	13	13.0	5.76 (0.75 – 44.07)	0.091
≥60	79	35.7	13	16.5	8.02 (1.04 – 61.34)	0.045
Gender						
Female	113	51.1	10	8.8	1	
Male	108	48.9	17	15.7	1.86 (0.85 – 4.07)	0.118
Histological Type						
Superficial extensive	134	60.6	13	9.7		
Nodular	63	28.5	14	22.2	2.25 (1.06 – 4.78)	0.035
Others	24	10.9	0	0.0	-	-
Location						
Head and neck	46	20.8	9	19.6	1	
Upper body	98	44.3	12	12.2	0.58 (0.24 – 1.38)	0.219
Members and other locations	77	34.9	6	7.8	0.36 (0.12 – 1.02)	0.055
Clark						
I, II e III	133	60.2	1	0.8	1	
IV	69	31.2	19	27.5	44.96 (6.01 – 336.26)	<0.001
V	19	8.6	7	36.8	54.60 (6.71 – 443.86)	<0.001
Breslow, mm						
<0.75	95	43	1	1.1	1	
0.75 – 1.50	59	26.7	3	5.1	4.73 (0.49 – 45.45)	0.179
1.51 – 2.25	20	9	2	10.0	9.68 (0.88 – 106.80)	0.064
2.26 – 3.00	16	7.3	6	37.5	48.28 (5.80 – 401.80)	<0.001
>3.00	31	14	15	48.4	62.24 (8.21 – 472.05)	<0.001

Ulceration						
Absent	149	67.4	5	3.4	1	
Present	72	32.6	22	30.6	10.23 (3.87 – 27.02)	<0.001
Lymphocyte infiltration						
Absent /Mild	104	52	3	2.9	1	
Moderate	74	37	9	12.2	4.57 (1.24 – 16.88)	0.023
Intense	22	11	5	22.7	9.21 (2.20 – 38.53)	0.002
Mitosis/mm^2						
Absent	102	53.4	2	2.0	1	
1 a 4	57	29.8	5	8.8	4.64 (0.90 – 23.90)	0.067
5 a 7	14	7.4	3	21.4	14.03 (2.34 – 84.25)	0.004
≥8	18	9.4	7	38.9	23.89 (4.96 – 115.16)	<0.001
TNM Stage						
I	132	59.7	1	0.8	-	
II	44	19.9	3	6.8	9.50 (0.99 – 91.44)	0.051
III	29	13.1	8	27.6	47.14 (5.86 – 379.06)	<0.001
IV	16	7.3	15	93.8	405.67 (51.44 – 3199.16)	<0.001

TNM: classification of malignant tumors (T: tumor, N: lymph nodes, M: metastases)
HR: hazard ratio, P: statistical significance obtained from a Cox regression model.

Figure 1. Disease-specific overall survival curve, cohort of patients with invasive melanoma, n = 221, Erechim.RS.

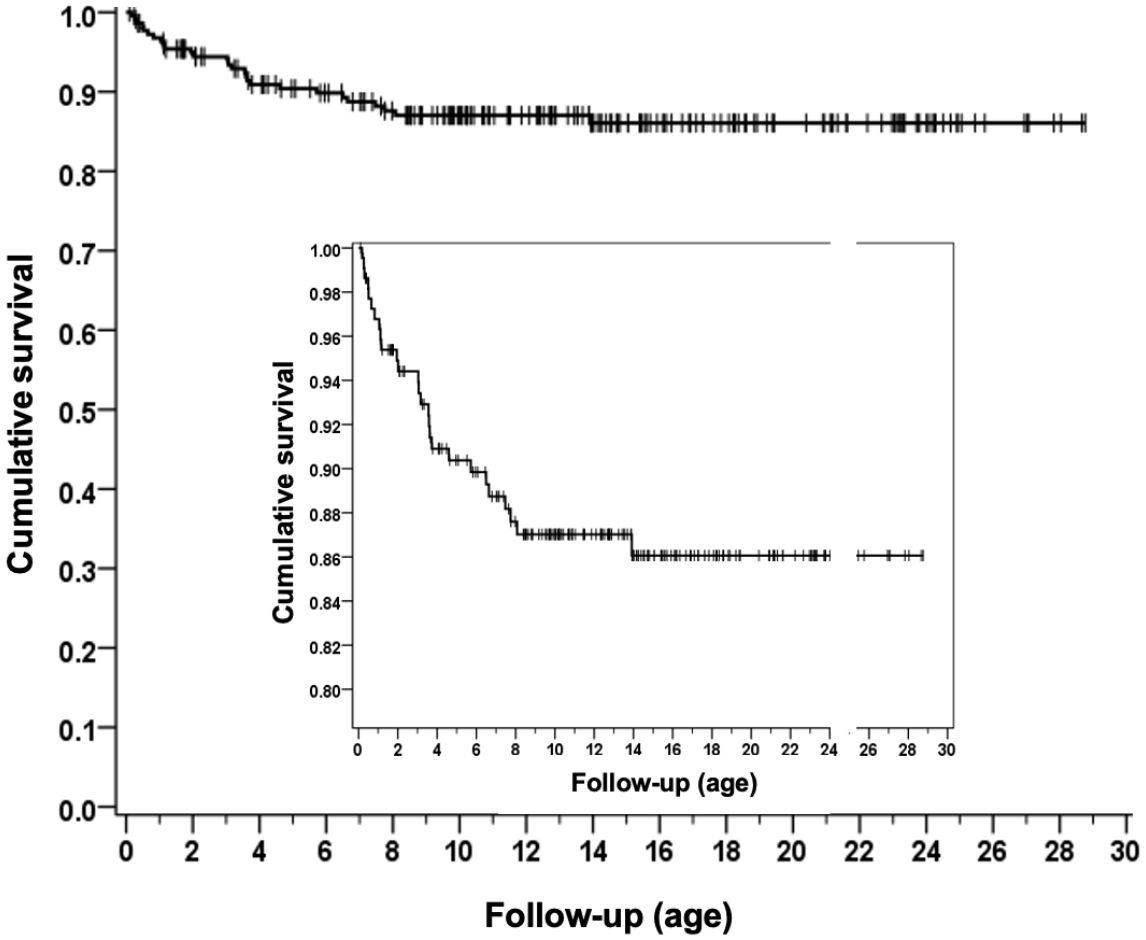
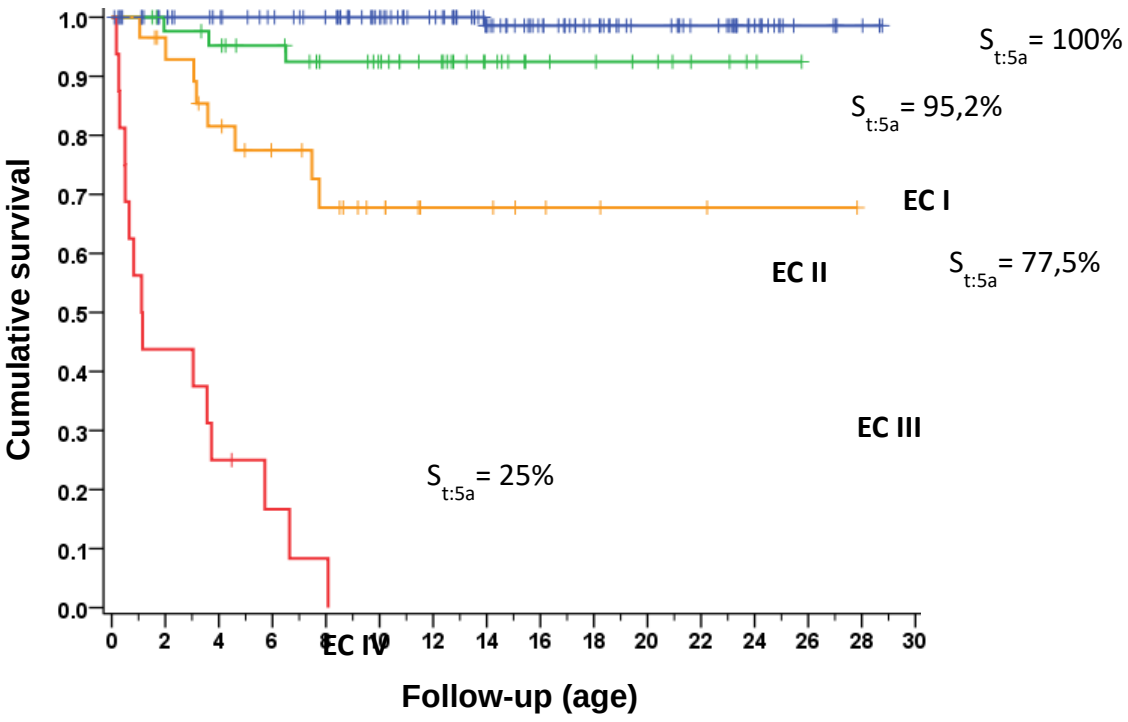


Figure 2. Disease-specific overall survival curves stratified according to TNM stage, cohort of patients with invasive melanoma, n=221, Erechim.RS.


Cumulative survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Follow-up (age)
EC I
EC II
EC III
EC IV
S t:5a = 100%
S t:5a = 95,2%
S t:5a = 77,5%
S t:5a = 25%