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Is survival from skin melanoma really improving? A retrospective cohort study in Gran Canaria Island (Spain)

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Dear Editors,

Improved survival from skin melanoma has been reported in recent years.¹ However, whether this survival improvement can be attributed to the emergence of new therapeutics or to a rise in the incidence of early forms of skin melanoma is controversial and unclear at the population level.² The objective of this study was to assess the evolution of skin melanoma survival on a Spanish island with universal healthcare, allowing full geographic coverage,³ and to evaluate the potential causes for any changes if encountered.

We conducted a multicentric retrospective cohort study in the two hospitals centralizing melanoma care in Gran Canaria (Canary Islands, Spain), reviewing the electronic records of patients diagnosed with skin melanoma between 2007 and 2018.⁴ Stage at diagnosis was updated to the 8th edition of the *American Joint Committee on Cancer*.⁵ To ensure a minimum follow-up time of 5 years, survival data was only calculated for patients diagnosed between 2007 and 2015. Vital status, information about any prescription of new therapies (targeted therapies or checkpoint inhibitors), and cause of death if applicable were checked for those patients. We obtained 5-year overall (OS) and melanoma-specific (MSS) survival rates with the Kaplan-Meier product-limit estimates of the survival function (Stata v16.0). We assessed the evolution of survival

rates over time by means of the annual percentage change (APC) with Joinpoint Regression Program v4.9.0.1. Then, to assess whether differences in survival over time existed, we split the sample into two periods of the same length (2007–June 2011 vs. July 2011–2015 diagnoses), calculated survival rates stratified by stage at diagnosis, and evaluated whether differences in prescriptions of new therapeutics existed between periods with the chi-squared test. Finally, we assessed the evolution of skin melanoma incidence in the study period. For incidence calculations only invasive skin melanomas were included,⁶ and the mid-year census population for each year was used as denominator.⁷ Ethical clearance was obtained (CEI/CEIm-HUGCDN 2019-515-1).

Between 2007 and 2015, 758 patients were diagnosed with invasive skin melanoma in Gran Canaria (Table 1). When analyzing crude data, survival improved in the study period, with 5-year MSS rates rising from 74.3% for patients diagnosed in 2007 (95% CI: 63.0%–82.6%) to 97.9% in 2015 (95% CI: 92.0%–99.5%), with an APC of +2.6% ($p = 0.001$). Similar results were obtained for OS (Figure 1a). However, when stratifying by stage at diagnosis, we did no longer find evidence of improved survival over time; all confidence intervals overlapped (Figure 1c, d). These figures also illustrate the excellent prognosis of stage I diagnosis, with 5-year survival rates close to 100%.

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TABLE 1 Characteristics of patients included in the survival analysis (residents in Gran Canaria diagnosed with skin melanoma in 2007–2015).

| | | Study period (Time of diagnosis) | | | |
|---------------------------------------|------------------------|----------------------------------|--------------------------|--------------------------|----------|
| Variable | Categories | All years n (%) | 01/2007–06/2011 n (%) | 07/2011–12/2015 n (%) | p-value* |
| Skin melanoma patients | | 758 (100) | 364 (100) | 394 (100) | – |
| Clinical characteristics at diagnosis | | | | | |
| Sex | Female | 408 (53.8) | 200 (55.0) | 208 (52.8) | 0.55 |
| Age at diagnosis, in years** | | 57.1 (16.7) | 54.4 (16.4) | 57.8 (16.9) | 0.27 |
| Body site | Trunk | 317 (41.8) | 150 (41.2) | 167 (42.4) | 0.46 |
| | Limbs (non-acral) | 262 (34.6) | 128 (35.2) | 134 (34.0) | |
| | Head & neck | 104 (13.7) | 45 (12.4) | 59 (15.0) | |
| | Acral (hand/foot) | 55 (7.3) | 28 (7.7) | 27 (6.9) | |
| | Other/NA | 20 (2.6) | 13 (3.6) | 7 (1.8) | |
| Stage | I | 517 (68.2) | 225 (61.8) | 292 (74.1) | 0.002 |
| | II | 125 (16.5) | 72 (19.8) | 53 (13.5) | |
| | III | 80 (10.6) | 43 (11.8) | 37 (9.4) | |
| | IV | 36 (4.7) | 24 (6.6) | 12 (3.0) | |
| Survival data | | | | | |
| Follow-up time, in years*** | | 4.3 (1.5) | 4.2 (1.6) | 4.4 (1.3) | 0.023 |
| Status at 5 years | Alive | 523 (69.0) | 227 (62.4) | 296 (75.1) | < 0.001 |
| | Death from melanoma | 116 (15.3) | 79 (21.7) | 37 (9.4) | |
| | Death from other cause | 76 (10.0) | 43 (11.8) | 33 (8.4) | |
| | Loss to follow-up | 43 (0.06) | 15 (4.1) | 28 (7.1) | |

*p-value: results of hypothesis testing between data from period 2007–2011 vs. 2011–2015: chi-squared test for differences in proportions, t-test for means (age). **Quantitative variables (age) are presented as: mean (standard deviation). ***Follow-up time presented as mean (sd), censored at 5 years.

Abbr.: NA, not available

After five years of follow-up, only 27 patients (3.6%) received new therapies (17 patients diagnosed in 2007–2011 vs. 10 in 2011–2015, representing 4.7% vs. 2.5%, respectively ($p = 0.11$)). For incidence calculations, data were available up to 2018. Between 2007 and 2018, 1,058 residents were diagnosed with melanoma, 55% of them with stage IA. Incidence increased by 2.4% per year in the study period ($p = 0.03$, Figure 1b). When stratifying by the earliest (IA) vs later stages (IB–IV), we found a steep APC for stage IA melanomas (+4.6%, $p = 0.004$), but no clear trend for more advanced stages, with an initial decline followed by an increase in recent years (Figure 1b).

Survival from skin melanoma improved in Gran Canaria by more than 20% between 2007 and 2015. However, when stratifying by stage at diagnosis, we did not find evidence of improved survival over time (Figure 1c, d). Slightly better MSS point estimates for all stages were achieved in recent years (Figure 1c), which may have marginally contributed to improved survival, but not be detected due to the limited sample size of our study. New therapies cannot explain the survival improvement seen in Gran Canaria, as only 27 patients (3.6%) received them, with no differences between periods. This is different than results from other population-based studies,⁸ which found an impact of new therapies, and could be explained by the limited availability of those

therapies in the years covered by the study. Meanwhile, the incidence rates of stage IA melanomas (of excellent prognosis) doubled, which did not happen with more advanced stages (Figure 1b). Massive sun exposure became popular in Spain in the 1970s and might partially explain this recent increase.⁹ Additionally, although skin cancer screening programs do not exist in Spain, the Spanish Academy of Dermatology (AEDV) has strived to promote public awareness and educational campaigns in the last two decades,¹⁰ which may have favored earlier diagnoses.

Overall, our results support a survival improvement from skin melanoma at the population level in Gran Canaria for 2007–2015 diagnoses, mostly driven by a sustained increase in very early diagnoses. The recent rise in the incidence of advanced forms is of concern and will need to be addressed.

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CONFLICT OF INTEREST

None.

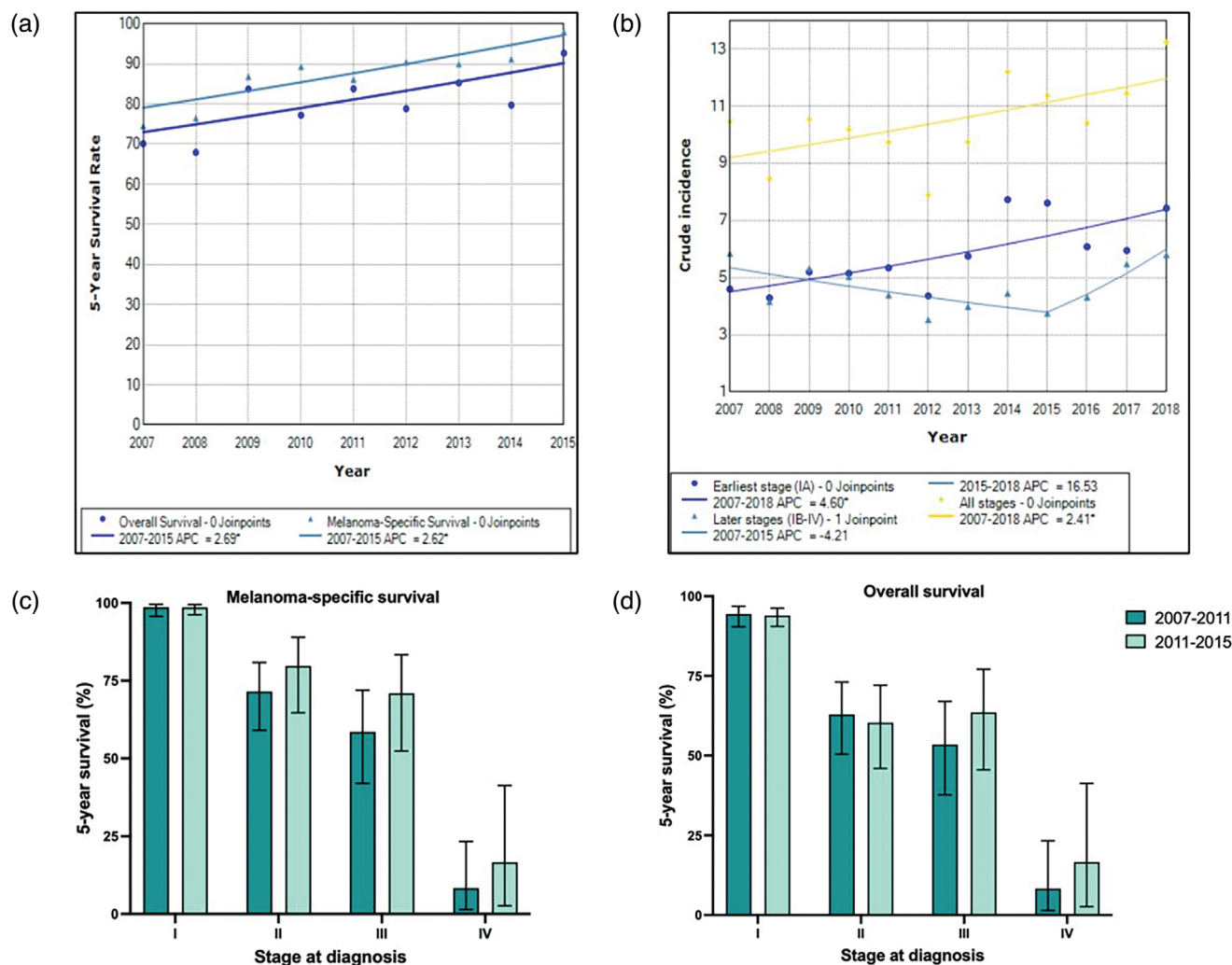




FIGURE 1 Evolution of survival and incidence of skin melanoma in Gran Canaria in 2007–2018. (a) 5-year survival rates of overall and melanoma-specific survival, per year of diagnosis; (b) Annual crude incidence rates of invasive skin melanoma (in cases per 100,000 population); Evolution of (c) melanoma-specific and (d) overall survival rates by stage at diagnosis, comparing patients diagnosed in 2007–2011 vs. 2011–2015. Survival rates obtained with the Kaplan-Meier product-limit estimates of the survival function; (a), (b) Figures obtained with Joinpoint Regression Program. Best fit of Joinpoint regression models estimating annual percent change (APC) is displayed. (a) 5-year survival rates (overall, dark blue and melanoma-specific, light blue) (b) Incidence data presented as cases per year per 100,000 population, for all stages (yellow) and stratified by earliest stage (IA, dark blue) vs later stages (IB to IV, light blue). (c), (d) Evolution of 5-year survival rates by stage at diagnosis and period of diagnosis (2007–2011 vs. 2011–2015), with error bars displaying 95% confidence intervals (c) melanoma-specific survival and (d) overall survival. Sample size for Figures c and d ($n = 758$ patients), in dark green: patients diagnosed in January 2007–June 2011; $n = 364$ with stage I = 61.8% of patients, II = 19.8%, III = 11.8%, IV = 6.6%. In turquoise: patients diagnosed in July 2011–December 2015; $n = 394$ with stage I = 74.1%, II = 13.5%, III = 9.4%, IV = 3%.

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