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Cutaneous Melanoma and Sentinel Lymph Node Biopsy; An Epidemiology Study of Population Level Data

L. Scanlon[1,2], A.J.P. Clover[2]

1. School of Medicine, University College Cork, Cork City, Ireland.
2. Department of Plastic Surgery, Cork University Hospital, Wilton, Cork.

Abstract

Aims

Cutaneous melanoma accounts for 90% of all melanoma cases diagnosed. In addition, the incidence of cutaneous melanoma is increasing by approximately 3-7% yearly, and it is the most rapidly increasing cancer diagnosed in white populations worldwide.

The aim of this study is to assess the survival benefit of Sentinel Lymph Node Biopsy (SLNB) in cutaneous melanoma in an Irish population.

Methods

Population based data was obtained from the National Cancer Registry of Ireland (NCRI) on all patients with a cutaneous melanoma diagnosed over a 20-year period 1994-2014 and predictors of Overall Survival (OS) were assessed.

Results

13302 patients were identified with a melanoma diagnosis between 1994-2014. OS varied with gender, age, smoking and marital status, anatomical location and TMN stage. 2196 (17%) patients underwent SLNB, which included 710 patients in the stage 1 melanoma category (<11% of this group).

Undergoing a SLNB was not an independent predictor of improved OS (p=0.440). However, a positive SLNB result was an independent predictor of OS (0.001).

Conclusion

This Irish population-based data re-affirms demographic indicators of poorer survival. A positive SLNB result indicates poorer survival; however, the precedent itself is not a predictor of OS.

Introduction

Skin cancer, particularly melanoma, is a significant problem in Irish Society and worldwide and overall incidence is rising in Ireland and worldwide at an alarming rate[1,2]. The National Cancer Registry of Ireland (NCRI) identifies, analyses and reports on the incidence and prevalence of all cancers diagnosed in Ireland. It is a national centralised database with staff based in hospitals throughout Ireland.

The NCRI predicts that the number of new skin cancers diagnosed each year in Ireland will double by 2040[1].

Cutaneous melanoma accounts for 90% of all melanoma cases diagnosed and is the most rapidly increasing cancer diagnosed in white populations worldwide[3,4]. It is particularly prevalent in Ireland compared to other European countries due to a combination of genetic predisposition to the phenotypic pale skin, light eye colour and high skin sensitivity to the sun and pulsed ultraviolet light[5,6,7].

The role of SLNB in the treatment of melanoma has been widely debated but remains a useful prognostic tool and is widely used as part of the staging process in patients diagnosed with intermediate thickness melanomas[8,9].
A positive result will often infer which patients require lymph node dissection and further treatment[10].

A number of studies have assessed the benefit of undergoing a SLNB in cutaneous melanoma patients; demonstrating a survival benefit in intermediate thickness melanoma patients who undergo SLNB, versus patient who undergo observation alone[10,11]. In addition, a number of studies have reported varying levels of survival benefit in patients who had negative SLNB results versus positive SLNB results[12,13,14,15,16].

To our knowledge, this is the first Irish population-based study, assessing the role of SLNB in melanoma.

Methods

Data was obtained from the National Cancer Registry of Ireland (NCRI) relating to all patients with cutaneous melanoma diagnosis over a 20-year period January 1994 to December 2014.

A descriptive analysis of patient demographics was undertaken, and univariate analysis was carried out using Kaplan Meier Estimate.

Analysis was carried out to assess whether age, sex, smoking status, marital status, anatomical location of the melanoma, melanoma stage, SLNB conducted and SLNB result were predictors of survival.

Pairwise comparisons were carried out for variables that consisted of more than two groups and a Bonferroni correction was applied to the univariate analyses, as necessary, to adjust the p-values and control for type 1 error that can arise as a result of making multiple comparisons.

Multivariate analysis was carried out using Cox regression analysis. Two models were undertaken using regression analysis to assess: if undergoing a SLNB predicts survival and if SLNB results predict survival after controlling for age group, gender, smoking status, marital status, cancer stage, anatomical location, and HSE region of residence.

All statistical analysis was carried out using SPSS software version 24.

A p value of <0.05 was considered to indicate a significant difference.

Results

13302 patients were diagnosed with cutaneous melanoma between 1994 and 2014.
OS reduced with increasing age between all age groups (all p<0.001) with the exception of the survival difference between <24 and 25-49 (p=0.899) (Table 1). Males had shorter OS compared to females (OS 65.4% M; 75.1% F) (Figure 1). and this was statistically significant (p<0.001).

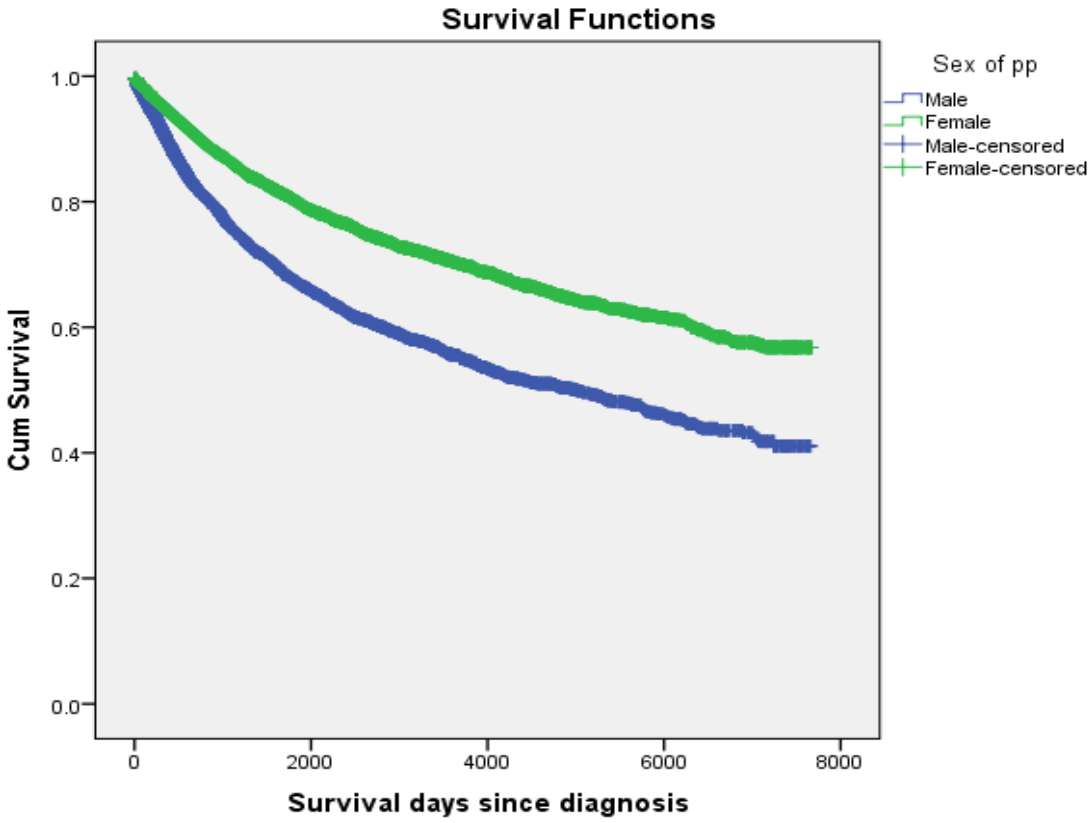

Figure 1: Overall Survival by Gender**.**

OS varied inversely with TMN stage; stage 4 had statistically shorter OS compared to all the other groups ($p<0.001$ for all comparisons), stage 3 had shorter OS compared to stage 1 and 2 ($p<0.001$ for both) and stage 2 had a statistically significant shorter survival time than stage 1 ($p<0.001$). While OS was higher for stage 0 or In-situ melanoma compared to stage 1, and stage 2, this was not statistically significant ($p=0.805$, $p=0.180$ respectively); however, when compared to stage 3, there was a statistically significant difference ($p=0.023$) (Table 1).

	Overall Survival
Gender	
Males	65.4%
Female	75.1%
Age (groups)	
<24	86.6%
25-49	87.7%
50-69	77.3%
70+	48.8%
Smoking Status	
Never	62.9%
Ex-smoker	55.8%
Current Smoker	58.7%
Marital Status	
Single	69.4%
Married	73%
Widowed	46.6%
Separated/Divorced	75.6%
HSE Region	
DNML	72.2%
DNNE	71.5%
South	71.5%
West	68.2%
Anatomical Location	
Head/Neck	62.3%
Trunk	77.7%
Upper Limb	77.5%
Lower Limb	75.2%
Overlapping/Unspecified	40.3%
Stage	
Stage 0	93.8%
Stage 1	86.4%
Stage 2	62.9%
Stage 3	49%
Stage 4	21.2%
SLNB Conducted	
Yes	72.9%
No	70.6%
SLNB Result	
Positive	59.2%
Negative	86.1%
Nodal Metastasis	
Yes	48.4%
No	77.2%

Table 1: Overall Survival and Patient Demographics and Clinical Characteristics**.**

In total, a relatively small number of patients 2196 (17%), underwent SLNB and this included 710 patients in the stage 1 melanoma group (<11% of this group).

There was a small variation in OS in patients who underwent SLNB compared to those who did not; 72.9% versus 70.6% and this was statistically significant for all stages with the exception of stage 1; stage 1 88.7% versus 86.1% (p=0.73), stage 2 76.7% versus 59.2% (p=0.001), stage 3 63.2% versus 42.4% (p<0.001), stage 4 29.6% versus 18.1% (p=0.002) (Figure 2). However, after controlling for marital status, age group, gender, smoking status, cancer stage, anatomical location, and HSE region, undergoing a SLNB was not a statistically significant independent predictor of OS (Hazard Ratio=1.052, 95% Confidence Interval 0.924-1.198, P=0.440).

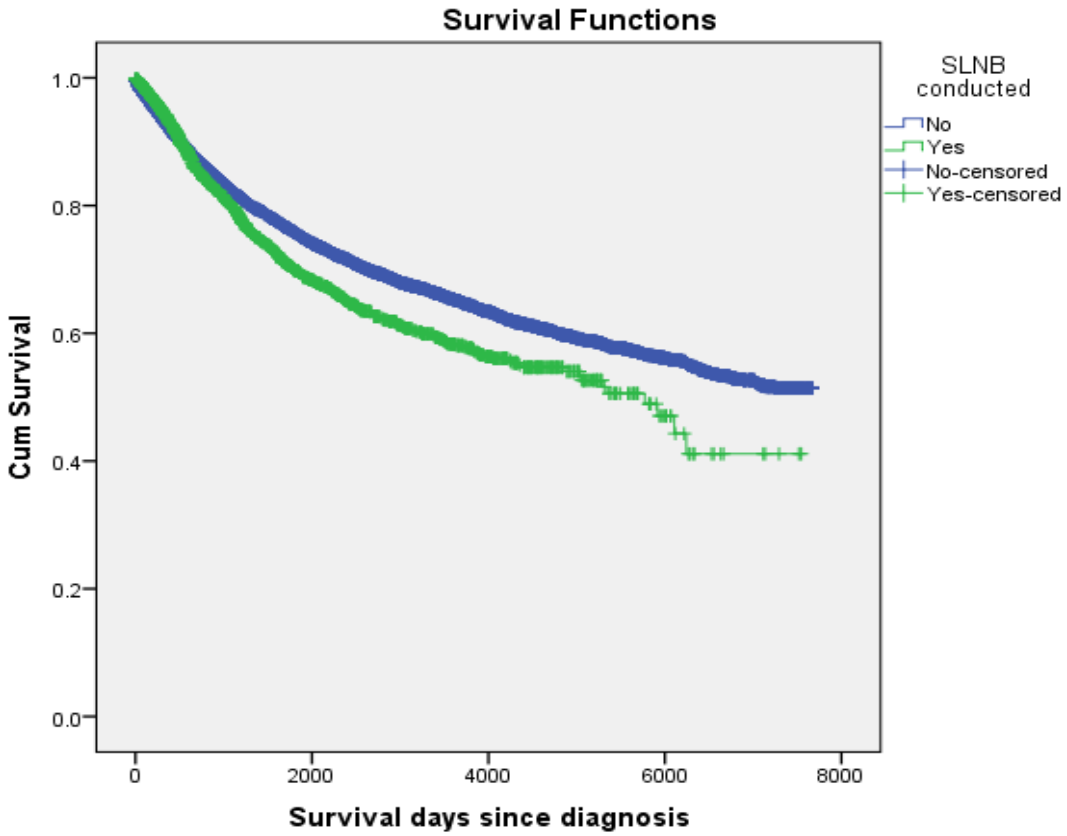

Figure 2: Overall Survival and SLNB conducted.

Patients with a positive SLNB had significantly shorter OS than those with negative SLNB results (p<0.001) (Figure 3) and this was an independent predictor of survival (Hazard Ratio 2.243, 95% Confidence Ratio 1.413-3.562, p= 0.001).

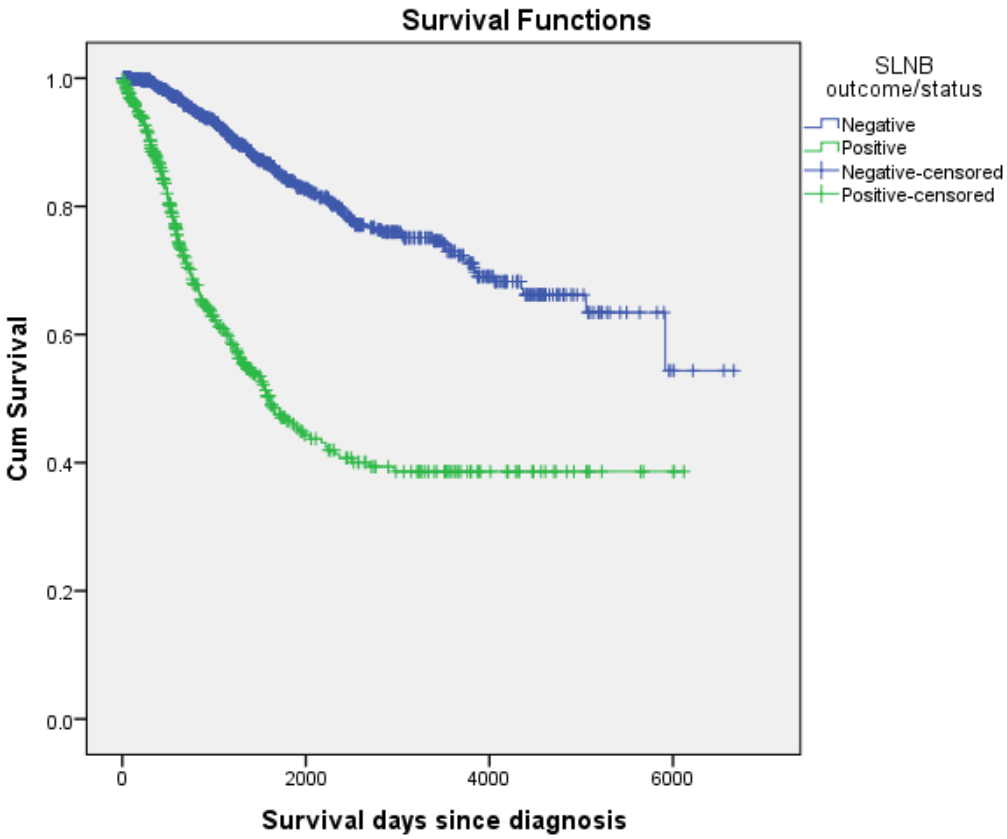

Figure 3: Overall Survival and SLNB result.

OS varied with anatomical location of the melanoma; patients in the overlapping/unspecified group had a statistically significant shorter OS compared to all other groups ($p<0.001$ for all comparisons) (Table 1). In addition, patients in the head/neck group had statistically shorter OS compared to the trunk ($p<0.001$), upper limb ($p<0.001$) and lower limb ($p<0.001$) (Table 1).

OS varied with smoking status; patients who had never smoked had longer OS compared to the other groups (never smoker versus current smoker $p=0.002$, never smoker versus ex-smokers $p<0.001$) (Table 1). Surprisingly, those who were current smokers had statically significant longer OS when compared to ex-smokers ($p=0.004$) (Table 1).

Married patients had statically significant longer survival than those who were single ($p=0.001$). Those who were widowed had a significantly shorter survival time compared to all other groups ($p<0.001$) while there was no significant difference between those who were separated/divorced and those who were married or single ($p=0.977$ and $p=0.189$ respectively) (Table 1).

Discussion

This is the first population level data specifically assessing OS in melanoma patients in the Irish population; it confirms and supports previously acknowledged independent predictors of OS.

This study found a number of patient demographics impacted on OS of cutaneous melanoma patients. Older age, male sex, positive smoking status and being widowed or single all predicted poorer OS. In addition, anatomical location, TNM stage and SLNB result all affected OS. Consistent with the published literature, OS varied inversely with age[10,13,17]. Recent studies have assessed the survival benefit of undertaking a SLNB in cutaneous melanoma and the survival benefit of positive versus negative SLNB results with a large variation in the survival benefit reported.

Our study found that male patients had shorter OS compared to their female counter parts; consistent with other large studies which have reported a similar, if less marked difference in prognosis based on patient gender[10,13,17,18]. Male patients generally tend to be more reluctant to engage in health screening which may account for this variation. High profile campaigns such as "Movember" and "Mens Health Week" have specifically targeted men in order to break down barriers and improve men's participation in health screening.

In our study, non-smokers had longer OS compared to current and ex-smokers (62.9% versus 58.7% and 55.8% respectively). Surprisingly, current smokers had longer OS compared to ex-smokers. This is consistent with Warren et al who found an increased Disease Specific Mortality (DSM) when comparing smokers to ex-smokers or non-smokers for all cancers[19]. OS is reduced in all smokers due to the numerous negative health effects of smoking, in addition, the poor wound healing associated with smoking could be particularly relevant in cutaneous melanoma patients with large surgical wounds, contributing to poorer OS in smokers. Smoking status is self-reported in the NCRI database which may limit the validity of this result.

Marital status has been widely reported as a prognostic indicator of survival and the reasons for this remain somewhat unclear[18,20]. We surmise that the social support involved in the detection and treatment of melanoma may contribute to the improved OS rates in patients who are/were married.

OS varied greatly based on anatomical location of the melanoma with overlapping/unspecified having by far the worst OS (40.3%). Head and neck melanomas were also associated with worse OS when compared to the trunk, upper limb and lower limb. Studies have reported that anatomic tumour location was a significant prognostic factor in melanoma, Tejera-Vaquerizo et al reported that melanoma of the head and neck was independently associated with lower melanoma specific survival (MSS)[18,21].

Not surprisingly, OS was inversely related to cancer stage, Cheng et al reported very similar figures to our study for stage 1-3, reporting 5 year MSS; stage 1 89%, Stage 2 61%, stage 3 40.6%, however Cheng et al reported much worse stage 4 survival of 8.2% compared to our study[10].
Cancer stage is inherently linked to prognosis and survival and, as expected, higher stage was associated with lower OS for all stages.

We noted a small but significant increase in OS in patients who underwent a SLNB compared to those who did not, 72.9% versus 70.6%; this concurs with other large population level studies[10,11].

OS in patients who underwent SLNB were also assessed for each cancer stage and the difference in OS was statistically significant for all stages with the exception of stage 1.

However, on further analysis after controlling for marital status, age group, gender, smoking status, cancer stage, anatomical location, and HSE region, the difference in OS in patients who underwent SLNB compared to those who did not, was not statistically significant. SLNB is recommended for patients with intermediate thickness melanomas and is often also undertaken in patients with a high suspicion of lymphatic spread clinically[22]. As such, it is not surprising that undertaking a SLNB does not predict improved OS.

Numerous studies have assessed the survival benefit of SLNB negative versus positive results in varying manners and with varying results, however, all agree that a negative SLNB result incurs a significant survival benefit compared to a positive SLNB result[12,13,14,15,16]. Our results concur with the literature; patients who had a positive SLNB result had a much lower OS compared to those with a negative SLNB result (59.2% versus 86.1% respectively). After controlling for patient demographics, SLNB result was a significant independent predictor of OS. Patients who had a positive SLNB result were 2.243 times more likely to die than those with a negative SLNB result.

As with cancer stage, a positive SLNB is inherently linked to poorer OS, defining it as a more advanced, aggressive disease stage and resulting in poorer OS.

The role of SLNB is changing; initially used as a diagnostic tool to indicate whether patients should proceed to completion lymph node dissection, large trials have failed to show a significant improvement in survival as a result of undergoing SLNB and increasingly the value of completion sentinel lymph node dissection is being questioned[23,24]. The treatment of melanoma has been undergoing a paradigm shift with the successful treatment of metastatic disease using immunotherapy. Large trials of neoadjuvant treatment are now reporting a survival advantage of neoadjuvant immunotherapy as opposed to observation[8,24]. As such the role of SLNB is becoming increasingly important as a gateway to neoadjuvant treatment.

This is a retrospective study from a pre-formed database and was limited to the information that had been collected by the NCRI.

In conclusion, cutaneous melanoma is a growing problem in Irish society. A number of factors predict OS of cutaneous melanoma patients. Older age, male sex, positive smoking status and being widowed or single all predict poorer OS. In addition, melanomas of the head and neck or overlapping/unspecified region, melanoma of a higher TNM stage and positive SLNB results all predicted lower OS rates.

Despite recent research to the contrary, undergoing a SLNB was not indicative of higher OS once other variables were controlled for.

Declaration of Conflicts of Interest:
The authors declare that there is no conflict of interest.

Corresponding Author:
Lorraine Scanlon,
School of Medicine,
University College Cork,
Cork City,
Ireland and Department of Plastic Surgery,
Cork University Hospital,
Wilton,
Cork.
E-Mail: LorraineScanlon@rcsi.ie

References:

1. Irish Cancer Society. About Skin Cancer [Internet]. Available from: http://www.cancer.ie/reduce-your-risk/sunsmart/skin-cancer#sthash.YDWkUmCC.dpbs Accessed 25/08/2015.
2. Gavin, A., Boyle, R., Donnelly, D., Donnelly, C., Gordon, S., McElwee, G. and O'Hagan, A., 2011. Trends in skin cancer knowledge, sun protection practices and behaviours in the Northern Ireland population. *The European Journal of Public Health*, 22(3), pp.408-412.
3. Leiter U, Garbe C. Epidemiology of Melanoma and Nonmelanoma Skin Cancer—The Role of Sunlight. In: Sunlight, Vitamin D and Skin Cancer Advances in Experimental Medicine and Biology, vol 624 Springer, New York, NY. vol 624. Springer, New York, NY; 2008. p. 89–103.
4. Ireland NCR. Cancer Trends National Cancer Registry Ireland. 2011;(7):2009–11.
5. Gu F, Chen T-H, Pfeiffer RM, Fargnoli MC, Calista D, Ghiorzo P, et al. Combining common genetic variants and non-genetic risk factors to predict risk of cutaneous melanoma. Hum Mol Genet. 2018;27(23):4145–56.
6. Pinault L, Bushnik T, Fioletov V, Peters CE, King WD, Tjepkema M. The risk of melanoma associated with ambient summer ultraviolet radiation. Heal Reports. 2017;28(5):3–11.
7. Arnold M, Holterhues C, Hollestein LM, Coebergh JWW, Nijsten T, Pukkala E, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. J Eur Acad Dermatology Venereol. 2014;28(9):1170–8.
8. Fioranelli M, Roccia MG, Pastore C, Aracena CJ, Lotti T. Completion dissection or observation for sentinel-node metastasis in melanoma. Dermatol Ther. 2017;30(6):2211–22.
9. Thomas JM, Patocskai EJ. The argument against sentinel node biopsy for malignant melanoma. Vol. 321, BMJ (Clinical research ed.). England; 2000. p. 3–4.
10. Chen J, Xu Y, Zhou Y, Wang Y, Zhu H, Shi Y. Prognostic role of sentinel lymph node biopsy for patients with cutaneous melanoma : A retrospective study of surveillance , epidemiology , and end-result population-based data. 2016;7(29).

11. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma. N Engl J Med. 2014;370(7):599–609.
12. Doepker MP, Thompson ZJ, Harb JN, Messina JL, Puleo CA, Egan KM, et al. Dermal melanoma: A report on prognosis, outcomes, and the utility of sentinel lymph node biopsy. J Surg Oncol. 2016 Jan;113(1):98–102.
13. Clary BM, Brady MS, Lewis JJ, Coit DG. Sentinel lymph node biopsy in the management of patients with primary cutaneous melanoma: review of a large single-institutional experience with an emphasis on recurrence. Ann Surg. 2001 Feb;233(2):250–8.
14. Kettlewell S, Moyes C, Bray C, Soutar D, MacKay A, Byrne D, et al. Value of sentinel node status as a prognostic factor in melanoma: prospective observational study. BMJ. 2006 Jun;332(7555):1423.
15. Roka F, Kittler H, Cauzig P, Hoeller C, Hinterhuber G, Wolff K, et al. Sentinel node status in melanoma patients is not predictive for overall survival upon multivariate analysis. Br J Cancer. 2005 Feb;92(4):662–7.
16. Biver-Dalle C, Puzenat E, Puyraveau M, Delroeux D, Boulahdour H, Sheppard F, et al. Sentinel lymph node biopsy in melanoma: our 8-year clinical experience in a single French institute (2002-2009). BMC Dermatol. 2012 Dec;12:21.
17. Banerjee M, Lao C, Wancata L, Muenz D, Haymart M, Wong S. Implications of age and conditional survival estimates for patients wiht melanoma. HHS Public Access Melanoma Res. 2016;26(1):69–81.
18. Xing Y, Chang GJ, Hu C-Y, Askew RL, Ross MI, Gershenwald JE, et al. Conditional survival estimates improve over time for patients with advanced melanoma: results from a population-based analysis. Cancer. 2010;116(9):2234–41.
19. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J Cancer. 2013;132(2):401–10.
20. Weiss NS, Flannery JT. The relationship of marital status to survival from melanoma. Cancer. 1978;42(1):296–8.
21. Tejera-Vaquerizo A, Nagore E, Puig S, Robert C. Effect of time to sentinel-node biopsy on the prognosis of cutaneous melanoma. Antonio. EUr J Cancer. 2015;51(13):277–94.
22. Rubinstein JC, Han G, Jackson L, Bulloch K, Ariyan S, Narayan D, et al. Regression in thin melanoma is associated with nodal recurrence after a negative sentinel node biopsy. Cancer Med. 2016;5(10):2832–40.
23. Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer N, Berking C, 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.
24. Spagnolo F, Boutros A, Tanda E, Queirolo P. The adjuvant treatment revolution for high-risk melanoma patients. Semin Cancer Biol. 2019;59: 283-289.