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Association between tumor characteristics and second primary cancers with cutaneous melanoma survival: a nationwide cohort study

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ABSTRACT

The increased survival in malignant cutaneous melanoma (melanoma) is probably due to early diagnosis combined with improved treatment most recently. National health campaigns and screening programs for melanoma detection were started in Sweden several decades ago. We want to assess the influence of tumor characteristics, based on the TNM classification, and of second primary cancers on overall survival in melanoma. We used the Swedish Cancer Registry to assess all-cause survival in melanoma from 2003 to 2015. Hazard ratios (HRs) were estimated using multivariable Cox regression models. A total of 19,773 melanoma patients were diagnosed with TNM data. Survival showed a strong improving trend over time (P-trend<0.001). T1a was the most common classification (48.0% of all) while higher T class associated systematically with worse survival (P-trend<0.001). For distant metastases the HR was 3.17, accounting for 0.9% of the patients. Any types of second primary cancers, other than melanoma, were associated with an HR of 2.00, accounted for 6.7% of all cases. Even if melanoma survival in Sweden ranks among the best national rates, the large percentage of patients advanced tumors (T3b, T4a and T4b, 17%) and 21% of deaths with T1a call for improved preventive and follow-up strategies.

Key words: TNM, tumor characteristics, metastasis, prognosis, survival.

Significance

The positive trend in melanoma survival has stalled in USA and Sweden. Here the influence of tumor characteristics on overall survival was assessed based on the TNM classification. The three highest T classes (T3b, T4a and T4b) accounting for 16.8% of all melanoma showed respective hazard ratios as 3.71, 4.37 and 5.90 against T1a. The large percentage of melanoma with advanced tumors may indicate flaws in preventive strategies. Rethinking education and awareness campaigns might be useful.

INTRODUCTION

Five-year survivals in white American patients with malignant cutaneous melanoma (subsequently 'melanoma') have improved from about 80% in 1975 to 90% by 2012 while there has been an increase in incidence (Jemal et al., 2017). A similar positive trend has also been observed in Europe (Crocetti et al., 2015; Lyth et al., 2015). Survival is critically dependent on whether the tumor is localized (96%), or spread to distant sites (41%), according to a US study, but even for thick localized tumors survival is decreased (Lo et al., 2018; Pollack et al., 2011). The reasons for the positive development are not entirely clear but tumor thickness is strongly related to survival and the overall tumor thickness has generally decreased in USA and parts of Europe (Lyth et al., 2015; Robsahm et al., 2018; Shaikh et al., 2016). However, there are indications that the positive trend in survival has stalled in USA and Sweden, suggesting the importance of novel strategies for early diagnosis (Jemal et al., 2017; Lyth et al., 2015). It is possible that therapy has also contributed to favorable prognosis even though the successes in targeted therapies including immunotherapy in metastatic melanoma may not yet be evident at the population level (Eggermont et al., 2014; Hartman and Lin, 2019; Schadendorf et al., 2018). Favorable trends in survival will inevitably result in an increased likelihood of second primary cancers (SPCs). According to a recent Swedish study, SPCs, including second melanoma, were diagnosed in 13.3% of melanoma patients and these were often found to be the causes of death (Chattopadhyay et al., 2019).

In the present study we want to characterize the influence of tumor thickness and ulceration on survival in melanoma patients. In multivariable analyses we want to compare survival depending on tumor characteristics, locoregional and distant metastases, including patients with second melanoma or other SPC.

METHODS

This is a national cohort study based on Swedish Cancer Registry where data for first melanoma and any subsequent cancers were obtained recording cancers according to the International Classification of Diseases 7th revision (ICD-7, code 200 for cutaneous melanoma) and later revisions. The clinical TNM classification system was introduced in the registry in 2002/2003, due to which not all hospitals

started at that time. A number of 19,838 (69.1%) patients with TNM classification were identified among 28,716 melanoma patients from 2003. After excluding 65 melanoma patients with unspecified tumor thickness (Tx), the total number of patients in the study was 19,773. Melanoma staging followed principally that of the American Joint Committee on Cancer (AJCC) sixth edition, published in 2001 (Balch et al., 2001). Towards the end of the study period the AJCC seventh edition was taken to use with the basic difference for the present study that an index for mitotic rate was introduced as an additional distinction between T1a and T1b (Balch et al., 2009). The exact timing of the switch to the seventh edition throughout the country is not known but in the national care program for melanoma, published in May 2013, the seventh edition was recommended as basis of classification (Nationellt vårdprogram malignt melanom – kortversion ISBN: 978-91-86929-09-1 Maj 2013). Nevertheless, considering the relatively good survival in melanoma overall we can assume that practically all melanoma deaths in the present study with follow up until the end of year 2015 were in patients who were classified according to the sixth edition.

Using the sixth edition, tumor thickness (T1 ≤1mm, T2 1-2mm, T3 3-4mm and T4>4mm) together with ulceration status (a, no ulceration and b, ulceration) was classified into eight groups including T1a, T1b, T2a, T2b, T3a, T3b, T4a and T4b. We considered locoregional (N) and distant (M) metastases, denoted by N+ (N1, N2, N3) or M+ (M1, M2); Nx and Mx denote undefined metastatic status. We followed newly diagnosed patients with melanoma from 1st January 2003 until 31st December 2015 for diagnosis of any of the 35 different SPCs including second melanomas. The follow-up for survival was terminated at emigration, death, or 31st December 2015, whichever occurred earliest.

Hazard ratios (HRs) for overall survival were estimated with Cox regression, adjusted for gender, age at diagnosis (≤50, 51-60, 61-70, 71-80, 81-90 and ≥91years old), year of diagnosis (≤2005, 2006-2010 and 2011-2015), tumor thickness, ulceration and histology (superficial spreading, nodular, lentigo maligna and other melanomas) of the first melanoma, locoregional and distant metastasis and diagnoses of SPC. Hazards for patients with different baseline tumor thickness/ulceration were compared to patients with T1 and without ulceration (T1a, reference population). In the Cox model, the diagnosis of SPC was treated as a time-dependent variable in order to avoid the immortal time

bias (Anderson et al., 1983). Trend test was performed by considering groups of variable of interest as continuous variables. Kaplan-Meier survival curves stratified by tumor thickness and ulceration were generated for patient with and without SPC.

All the statistical tests were two sided and P < 0.05 was considered significant. Analyses were done with R version 3.4, SAS version 9.4 and Stata version 15.1. 'coxph' function of 'survival' package in R was used to perform Cox regression with time-dependent variable.

The study was approved 6 February 2013 by the Ethical Review Board of Lund University (Dnr 2012/795), without requirement for informed consent. Through advertisements in the major newspapers people could chose to opt out before the research database were constructed. The project database is located at Center for Primary Health Care in Malmö, Sweden.

RESULTS

A total of 19,773 patients were diagnosed with first melanoma with TNM staging from 2003 to 2015. Gender, age at diagnosis and year of diagnosis, TNM classification, histology and SPC diagnosis of patients are shown in Table 1. Most of the patients were diagnosed with T1a (48.0%), followed by T2a (16.3%). Because of the clinical TNM classification, undefined (Nx, Mx) cases were common and confirmed locoregional (2.5%) or distant metastases (0.9%) were rare. Superficial spreading melanoma accounted for more than half of the patients (58.8%). During follow-up time, 2030 (11.3%) patients developed SPCs, including 706 (3.6%) second melanomas.

Table 2 displays how demographic and clinical factors affect survival of melanoma patients in multivariable Cox analyses. Patients with older age at diagnosis had poor survival; for age over 91 years, the HR increased up to 15.98 (95%CI: 13.08-19.51). Female patients were observed with better prognosis compared to males (0.69, 0.64-0.74). HRs showed a periodic decline in risk from the reference rate of 1.00 in 2003-2005 to 0.73 in 2006-2010 and 0.51 in 2011-2015 (P-trend <0.001); for the patients diagnosed in 2011-2015, the HR (0.51, 0.45-0.59) was approximately 50% of that for those diagnosed before 2006. Compared to patients diagnosed with T1a, the HR for patients with T1b melanoma was 1.44 (1.20-1.73) and it increased monotonously to 5.90 (5.17-6.74) for patients with

T4b. It is noteworthy that T1a accounted for 20.9% of all deaths, and the three T classes (T3b, T4a and T4b) combined account for another 48.1% with respective high HRs of 3.71, 4.37 and 5.90.

The trend test for tumor thickness and ulceration showed high significance (P-trend <0.001, Table 2). Patients with locoregional (2.24, 1.82-2.75) and distant metastases (3.17, 2.40-4.19) had poorer prognosis than those without. Note that for many patients metastatic status was undefined (Nx or Mx) and the HRs were low (1.29 and 0.92, respectively), indicating that most of these patients had no metastases. Nodular melanoma (NM, 1.14, 1.03-1.26), and lentigo melanoma (1.20, 1.02-1.41) showed worse survival than superficial spreading melanoma (SSM); the other histology types additionally included undefined histologies (1.10, 1.00-1.22). The increased HR for nodular melanoma was only modest, in spite of the number of cases, which equaled that of superficial spreading melanoma; the reason was the high age of patients with nodular melanoma.   Patients with second melanoma had poorer survival (1.48, 1.23-1.78) compared to patients with only first melanoma. The survival was worse for patients with other SPC (2.00, 1.75-2.30) which accounted for 6.7% of all cases. The trend test for SPC diagnosis was highly significant (P-trend <0.001).

Kaplan-Meier survival probability stratified by tumor T class and ulceration in patients without SPC diagnosis is displayed in Figure 1. Consistent with Table 2, the worse survival (25% in 12 years) was observed for patients with thick tumors and ulceration. Patients with T1a had a survival of close to 90% after the 12-year follow-up time, and somewhat better than that of patients with T1b and T2a. Survival curves for T2b and T3a clustered close to each other as did those for T3b and T4a. Kaplan-Meier survival plots were also generated for patients with SPC diagnosis (Figure 2). The differences in survival probability between various tumor T classes in patients with SPC were not as apparent as that in patients without. For the same tumor T class and ulceration, survival probabilities in patients with SPC were generally lower than those without.

DISCUSSION

In this nationwide cohort study including 19,773 melanoma patients with and TNM data, we found that old age at diagnosis and male sex were associated with decreased survival. Survival showed a strong improving trend over time. Higher T class associated systematically with worse survival. The

three highest T classes (T3b, T4a and T4b), totally accounting for 16.8% of all patients, and showed the respective HRs were as high as 3.71, 4.37 and 5.90. For distant metastases the HR was 3.17, accounting for 0.9% of the patients. Second primary cancers other than melanoma were associated with decreased survival, accounted for 6.7% of all cases.

Surgery is the main treatment modality for melanoma and a study published in 2016 based on the Stockholm Melanoma Register showed that 98.9% of all patients underwent surgery at baseline (Rockberg et al., 2016). However the percentage was stage dependent and for stage IV (metastatic) patients it was only 52.2% but such patients with distal metastases accounted for only 1.3% of all patients. Targeted therapy with BRAF and MEK inhibitors and immunotherapies with checkpoint inhibitors have been recent highlights in the fight against melanoma death in metastatic disease (Eggermont et al., 2014; Schadendorf et al., 2018). The approval by the European Medicines Agency for BRAF was in 2012 and for the combo BRAF+MEK it was 2014. The first checkpoint inhibitor ipilimumab was approved in Europe in 2011 but the use has been limited because of toxicity and limited effectiveness (Rozeman et al., 2018). It was not until 2015 when nivolumab and pembrolizumab were approved that the use of checkpoint inhibitors started to increase. The periodic HRs in Table 2 showed a time-dependent decline in risk from a reference rate of 1.00 in 2003-2005 to 0.73 in 2006-2010 and 0.51 in 2011-2015 (P for trend <0.001). BRAF inhibitors may have contributed to the decline in the last period but probably other factors play the main role (Helgadottir et al., 2018). Earlier diagnosis of thinner lesions contributes to improved survival but there is concern that screening campaigns may lead to overdiagnosis which, however, in the case of melanoma is a minor issue (Breitbart et al., 2012; Crocetti et al., 2015; Lyth et al., 2015; Shaikh et al., 2016; Weyers, 2018).

The present results emphasize the role of tumor characteristics in influencing survival. In the multivariable analysis, three T classes (T3b, T4a and T4b), combined accounting for 16.8% of all patients were associated with worse survival. The HR for patients with distant metastases, 0.9% of all patients, was 3.17 in this study. The latter percentage is an underestimate because of many patients presented with an undefined metastasis status at diagnosis. However, two Swedish studies based on ad hoc melanoma registers reported proportion for patients with distant metastasis of 1.3 and 0.7%

(Rockberg et al., 2016; Utjes et al., 2017). Of note, as we wanted to see the effects from SPC diagnosis, the present data included all deaths while some survival literature covers melanoma-specific survival. For example, a recent Norwegian study on melanoma-specific survival reported a HR of 16.82 for distant metastases and 9.68 for T4 class; the follow-up time was short from 2008 to 2015 which additionally emphasizes the role of metastases at diagnosis (Robsahm et al., 2018). While that study and a few others have considered survival in patients with second melanoma, our study is probably the only one so far considering other SPCs in the multivariable models (Utjes et al., 2017). SPCs other than melanoma may be highly fatal and they should be included on any cancer-related survival studies (Chattopadhyay et al., 2019).

In a European comparison on melanoma survival Sweden ranked the third after Northern Ireland and Switzerland (Crocetti et al., 2015). Yet, the present results call for novel approaches in melanoma prevention. In Sweden national multi-level melanoma prevention campaigns were started already in the late 1980s; these included education for physicians, nurses and the general population (Ringborg et al., 1991). Different screening approaches were tested at the population level (Tornberg et al., 1996). The results suggest that such programs do not reach all walks of life; low level of education was associated with reduced melanoma-specific survival, which was at least partially attributed to advanced stages at diagnosis (Eriksson et al., 2013). The present finding that 10.9% of melanomas present with T4 class, i.e., thicker than 4 mm and 2/3 of them with ulceration is another witness to a limited population penetrance of the Swedish health education, in spite of all efforts. One cost effective screening option would be to link skin examination to the national mammographic screening program which in Sweden is attended by 80% of the eligible women (Norfjord Van Zyl et al., 2018). Unfortunately, the 20% non-attendees are probably also a problem population for melanoma. As mortality in melanoma is lower for women than for men, alerting men would be particularly important. Skin examination should be part of regular (opportunistic) health examinations but again non-attendees are a likely risk group.

An important point is that in spite of the above discussion on deleterious survival consequences of higher T classes, the bottom line was that 21% of melanoma deaths were in patient with T1a staging, accounted for 48% of T class defined patients. This may raise concerns on the practical follow-up of

diagnosed patients, for which recommendations are given in the national care programs for melanoma (Wikstrom et al., 2018). In the program from year 2013, referred to in Methods, the recommendation for low-risk patients (T1a) was a single dermatological follow-up visit after 4 to 6 weeks following surgery. This recommendation is essentially repeated in the program from year 2017. Probably the patient was reassured that the risk is low and in so believing he may overlook signs of recurrent disease.

The strengths of the present study include nation-wide coverage of histologically verified melanomas and of deaths. This is the first study which included SPCs in the multivariable survival analysis, and in doing all-cause mortality was recorded instead of melanoma-specific mortality. The weaknesses are the relatively short follow-up which was due to the late collection of TNM data by the Cancer Registry. We only included the patients with TNM classification, which may introduce selection bias. Even though the nation-wide enactment of TNM classification could have been less than homogeneous, there is hardly any evidence of drastic change in treatment modalities during the initiation period. Tumor thickness is crucial and the T1 class is unable to gauge further details and these have been added into the later editions of the classification system. The start of the TNM coverage of the classification is random unlikely to be sensitive to selection bias.

In conclusion, the multivariable survival data showed that the three highest T classes, which accounted for 16.8% of all patients, were associated with worst survival. In spite of various melanoma-directed health campaigns many patients presented with delayed diagnoses. Mortality reducing melanoma prevention programs would require some novel approaches to reach the least health-conscious segments of the population. Better utilization of primary care clinics, of more widespread use of in vivo diagnostic technologies, and of new available smartphone "apps" may be helpful. For example, there are applications that can be used to indicate which moles might need treatment, but the challenge is how to get people-at-risk to use them (Marek et al., 2018b; Marek et al., 2018a). Finally, as 21% of deaths were found among T1a patients, a clinical follow-up plan should be devised in order to properly coop with this assumed 'low-risk' group.

Data Availability Statement

The data that support the findings of this study are available from Lund University but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Conflicts of Interest Statement

A.H. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Design: KH, GZ

Acquisition of data: JS, KS

Statistical analysis and interpretation: GZ, SC, KH, JS, KS, AS, AH.

Manuscript writing: KH and all other authors.

Approval of the final text: All authors

Figure legends

Figure 1 Survival probability stratified with tumor thickness and ulceration after diagnosis of first melanoma in patients without SPC diagnosis. SPC, second primary cancer, a, no ulceration, b, with ulceration.

Figure 2 Survival probability stratified with tumor thickness and ulceration after diagnosis of first melanoma in patients with SPC diagnosis. SPC, second primary cancer, a, no ulceration, b, with ulceration.

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Table 1 Demographic and clinical characteristics of melanoma patients

Characteristics		Number of cases	Proportion (%)
Age at diagnosis	≤50	5329	27.0
	51-60	3540	17.9
	61-70	4537	22.9
	71-80	3789	19.2
	81-90	2180	11.0
	≥91	3980	20.1
Gender	Male	9711	49.1
	Female	10062	50.9
Calendar year of diagnosis	≤2005	2409	12.2
	2006-2010	6812	34.5
	2011-2015	10912	55.2
Tumor staging (T)	T1a	9482	48.0
	T1b	1539	7.8
	T2a	3227	16.3
	T2b	774	3.9
	T3a	1445	7.3
	T3b	1161	5.9
	T4a	706	3.6
	T4b	1439	7.3
Locoregional metastasis (N)	N0	14084	71.2
	N+	488	2.5
	Nx	5201	26.3
Distant metastasis (M)	M0	13690	69.2
	M+	169	0.9
	Mx	5914	29.9
Histology	SSM	11628	58.8
	NM	3109	15.7
	LMM	1067	5.4
	Other and missing	3969	20.1
SPC diagnosis	Without SPC	17743	89.7
	Second melanoma	706	3.6
	Other SPC	1324	6.7

N+ includes N1, N2 and N3; M+ includes M1 and M2

SPC, second primary cancer

SSM, superficial spreading melanoma, NM, nodular melanoma, LMM, lentigo maligna melanoma, other melanomas include acral lentiginous melanoma, desmoplastic melanoma and some others.

Table 2 Multivariable Cox proportional regression model for survival in melanoma patients

Covariate		No. at risk	No. of death	HR	95%CI		P-value
Age at diagnosis	≤50 (ref)	5542	237	1.00	-	-	
	51-60	3840	278	**1.42**	1.20	1.70	<0.001
	61-70	5142	518	**2.04**	1.75	2.39	<0.001
	71-80	4351	860	**3.71**	3.19	4.32	<0.001
	81-90	2497	1022	**8.46**	7.26	9.85	<0.001
	≥91	430	267	**15.98**	13.08	19.51	<0.001
	P-Trend						<0.001
Gender	Male (ref)	10909	1888	1.00	-	-	
	Female	10893	1294	**0.69**	0.64	0.74	<0.001
Calendar year	≤2005 (ref)	2403	722	1.00	-	-	
	2006-2010	7691	1585	**0.73**	0.65	0.81	<0.001
	2011-2015	11708	875	**0.51**	0.45	0.59	<0.001
	P-Trend						<0.001
Tumor staging	T1a (ref)	10384	664	1.00	-	-	
	T1b	1710	127	**1.44**	1.20	1.73	<0.001
	T2a	3574	349	**1.46**	1.28	1.66	<0.001
	T2b	865	142	**2.38**	1.98	2.86	<0.001
	T3a	1635	369	**2.71**	2.36	3.11	<0.001
	T3b	1284	425	**3.71**	3.23	4.27	<0.001
	T4a	780	313	**4.37**	3.72	5.13	<0.001
	T4b	1570	793	**5.90**	5.17	6.74	<0.001
	P-Trend						<0.001
Locoregional metastasis	N0 (ref)	15432	1700	1.00	-	-	
	Nx	5839	1225	**1.29**	1.11	1.50	<0.001
	N+	531	257	**2.24**	1.82	2.75	<0.001
Distant metastasis	M0 (ref)	14977	1661	1.00	-	-	
	Mx	6639	1395	0.92	0.79	1.07	0.28
	M+	186	126	**3.17**	2.40	4.19	<0.001
Histology	SSM (ref)	12816	1168	1.00	-	-	
	NM	3444	1130	**1.14**	1.03	1.26	0.01

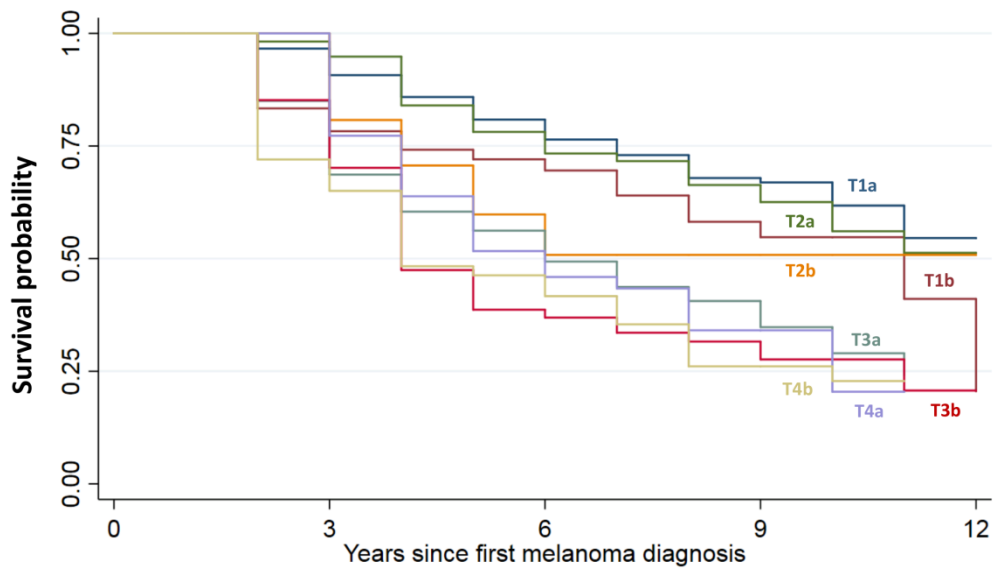|							
	LMM	1195	202	**1.20**	1.02	1.40	0.03
	Other	4347	682	**1.10**	1.00	1.22	0.05
Diagnosis of SPC	Without SPC	17743	2644	1.00	-	-	
	Second melanoma	706	133	**1.48**	1.23	1.78	<0.001
	Other SPC	1323	405	**2.00**	1.75	2.30	<0.001
	P-Trend						<0.001

N+ includes N1, N2 and N3; M+ includes M1 and M2

HR, hazard ratio, CI, confidence interval, SPC, second primary cancer

SSM, superficial spreading melanoma, NM, nodular melanoma, LMM, lentigo maligna melanoma, other melanomas include acral lentiginous melanoma, desmoplastic melanoma and some others.
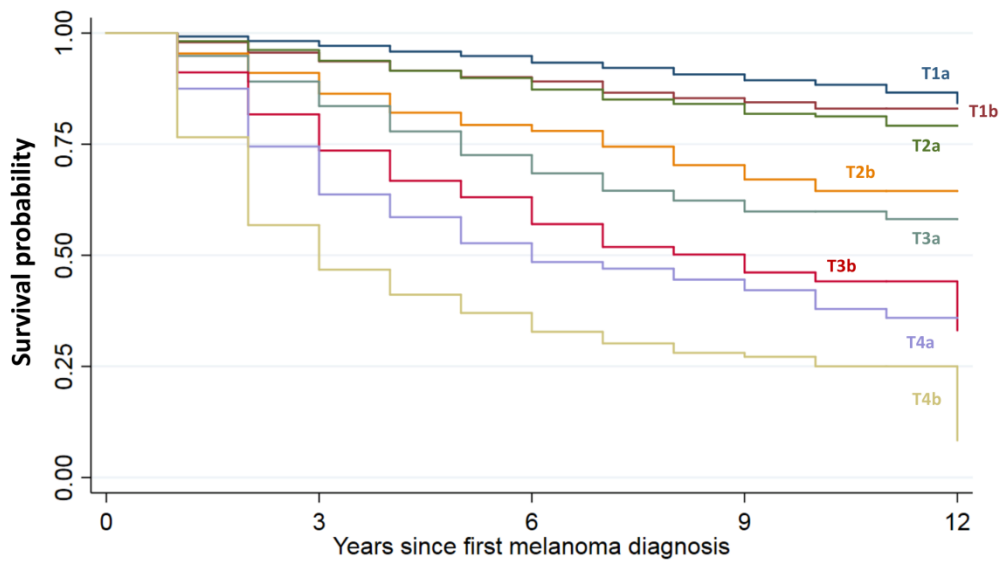
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