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Short Communication

Mortality Rates in Cutaneous Melanoma more than Halved from 2009 to 2017: Revolutional Break-Through in Melanoma Therapy or Statistical Artifact?

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Abstract

Based on the leading AJCC melanoma staging system references from 2009 Balch et al. and 2017 Gershenwald et al., comparison of mortality rates (for 10 years and 5 years, resp.) exhibit a surprising decrease by a factor of about 2.5 for different cutaneous melanoma stages, e.g. IB, IIA, IIB, IIC, IIIA, and IIIB, whereas the respective comparison between the former references from 2001 Balch et al. and 2009 Balch et al. amounts only to a factor of about 1.15.

An improvement so dramatic in a short time interval of 8 years might suggest a revolutional break-through in melanoma treatment regimes, perhaps unsurpassed in the history of oncology. However, this striking phenomenon lacks convincing explanation up to now. Neither the hypothesis of stage migration (mis-classification) in former patient data, nor the impact of novel therapies, such as checkpoint inhibitors, can be sufficiently validated. Therefore it seems important that this embarrassing discrepancy should be taken seriously as a matter of revision and re-evaluation and deeper investigation.

Materials and Methods

The data used in the present study are based on the leading publications by Balch et al. [1] and Balch et al. [2] and by Gershenwald et al. [3].

In order to clarify the discrepancies between the 2017 and the 2009 papers it makes sense to replace empirical Overall Survival (OS) rates p_{OS} by complementary death rates or mortality rates: $p_M = 1 - p_{OS}$.

For example: an improvement of survival rate from 0.80 to 0.90 looks small, however complementary mortality rates' reduction from 0.20 to 0.10 signifies that the number of deaths is halved, which means a great achievement. Moreover: death and metastatic recurrence are "positive" events, survival is not.

In Table 1 the 10 years survival rates for stages IB, IIA, IIB, IIC, IIIA, and IIIB are listed according to the data published in the referenced papers. The corresponding mortality rates are listed in Table 2, and additionally the virtual Improvement Factors IF, defined as the quotients of the mortality rates from 2001 and 2009 (5th column) and the mortality rates' quotients from 2009 and 2017 (6th column), respectively. Stage IA is omitted due to small mortality rates ≤10% which would imply large propagation of reading and rounding errors, and stage IIIC is omitted because the redefinition in 2017 will not permit reliable quantitative comparison.

The selection criteria in the present study have been chosen such that the selected stages are affected as little as possible, if that, by the redefinitions in 2017.

Table 1: Overall Survival (OS) probability within 10 years according to AJCC publication.

Melanoma Stage	Overall Survival (OS) probability within 10ys / % according to AJCC publication					
	(2001)			(2009)		(2017)
	(# p)	OS	(± SD)	(# p)	OS	(# p) OS
I B	(4665)	81	(± 1.2)	(8918)	84	(5749) 94
II A	(2675)	64	(± 1.9)	(4644)	66	(2338) 88
II B	(2086)	52	(± 2.2)	(3228)	56	(1688) 82
II C = T4b	(978)	32	(± 2.1)	(1397)	39	(691) 75
III A	(382)	60	(± 5.3)	(1196)	68	(1006) 88
III B	(543)	38	(± 5.7)	(1391)	43	(1170) 77

Abbreviations: # p: Number of Patients Evaluated; OS: Overall Survival; SD: Standard Deviation

Comments: Melanoma-specific OS data had been obtained using Kaplan-Meier statistics.

(#p) and OS data in second column block are read from survival curves in Figures 3 and 5 in Balch et al. [1].

SD values are estimated from Table 3 in Balch et al. 2001; SD data are missing in the 2009 and 2017 papers.

(#p) and OS data in third column block are read from survival curves in Figure 1 in Balch et al. [2].

(#p) and OS data in forth column block are tabulated in Figures 6 and 7 in Gershenwald et al. [3].

Stage III C is omitted due to redefinition in Gershenwald et al. [3].

Results

The data from 2009 and 2001 seem to be consistent in that the survival and mortality rate data are of the same magnitude and the data from 2009 show only a slight improvement by a factor of about 1.15 (± 0.1) with respect to the data from 2001 for all investigated

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stages. However, from 2009 to 2017 a virtually huge improvement by a factor of 2.5 (± 0.5), is showing up for all the investigated stages from IB up to IIIB both for the 10 years death rates (Table 2) and the 5 years ones (not tabulated).

Table 2: Mortality Rate and Virtual Improvement Factor.

Melanoma Stage	Mortality Rate (MR) within 10ys / % according to AJCC publication			Virtual Improvement Factor (IF)	
	(2001)	(2009)	(2017)	(2001)/(2009)	(2009)/(2017)
	MR (± SD)	MR (± SD)	MR (± SD)	IF (± SD)	IF (± SD)
I B	19 (± 1.2)	16 (± 0.9)	6 (± 1.1)	1.2 (± 0.1)	2.7 (± 0.5)
II A	36 (± 1.9)	34 (± 1.4)	12 (± 2.0)	1.05 (± 0.07)	2.8 (± 0.5)
II B	48 (± 2.2)	44 (± 1.8)	18 (± 2.5)	1.1 (± 0.07)	2.4 (± 0.35)
II C = T4b	68 (± 2.1)	61 (± 1.8)	25 (± 2.5)	1.1 (± 0.05)	2.4 (± 0.3)
III A	40 (± 5.3)	32 (± 3.0)	12 (± 3.3)	1.25 (± 0.20)	2.7 (± 0.75)
III B	62 (± 5.8)	57 (± 3.6)	23 (± 3.9)	1.1 (± 0.12)	2.5 (± 0.45)

(SD) in 2nd column block obtained from Table 3 in Balch et al. [1].
(SD) in 3rd and 4th column block is estimated using the rule of inverse square root (with respect to number of patients).
(SD) in 5th and 6th column block results from error propagation.

Discussion

This striking phenomenon lacks convincing explanation up to now. In Gershenwald et al. [3] some possible causes are mentioned, such as mis-classification in the 2009 data or introduction of novel efficient therapy methods (such as checkpoint inhibitors), which might partly explain the dramatic reduction in death rates. In the following the two theses will be tested.

Thesis: Stage Migration

Stage-migration, i.e. mis-classification in part of the 2009 data, might explain the high death rates in the 2009 paper compared with the recent 2017 paper.

Counter-validation: Let us take for example stage IIIB and 10 years' death rates from 2017 data for granted. Let us further assume that part of the IIIB classifications in 2009 should have been in fact IIID (a new category of bad prognosis, introduced in 2017).

Question: What portion "y" of miss-classifications could explain the high death rate of 0.57 (read from Figure 1D in the 2009 paper)?

Answer: The corresponding 10 years death rates in the 2017 paper are 0.23 for stage IIIB and 0.76 for stage IIID (read from Figure 7 in the 2017 paper).

Thus the following equation for the unknown portion "y" of mis-classifications reads: 0.57 = (1 - y) 0.23 + y 0.76 = 0.23 + 0.53 y; from this follows: y=0.64.

Consequence: In order to "explain" the large virtual "improvement" from 2009 to 2017 by stage migration, it must be assumed that about two thirds of the diagnostic staging in 2009 had been false; i.e. most multi-node infiltrations (according to definition of melanoma stage IIID) had been missed. Surely, nobody would accept such poor state of the art of oncological diagnostics. Therefore this thesis fails as a convincing explanation.

Thesis: Novel Therapies

Use of novel highly efficient therapies, such as based on checkpoint inhibitors, might explain the decrease of death rates. However, since Pembrolizumab and Nivolumab have got approval by the FDA not before 2014 as therapy in advanced melanoma, the impact on 10 years mortality rates can be assumed as small up to now. Therefore also the second thesis fails.

In a recent publication by Eggermont et al. [4] a randomized, placebo-controlled phase 3 trial using Ipilimumab as adjuvant therapy in patients with resected stage III melanoma is reported. In that trial, at 5 years follow-up use of Ipilimumab resulted in a 65% overall survival rate *vs.* 54% with placebo. These survival data are more consistent with the 2009 AJCC paper than with the 2017 one. With respect to 5 years' death rates the improvement by Ipilimumab therapy *vs.* placebo was by a factor of 1.3. This is also far away from factors about 2.5, resulted from the 2009 *vs.* 2017 comparison.

Addendum

Our estimation of virtual Improvement Factors IF is of course affected by the statistical uncertainty of the mean Overall Survival (OS) rates given in the literature. But only in Balch et al. [1] Standard Deviations (SD) of the calculated mean OS rates are given, regrettably not in the 2009 and 2017 papers. To overcome this lack of information one can try to estimate the missing standard deviations using the "inverse square root rule", i.e. that the SD of the statistical mean of independent Random Variables (RV) behaves as the inverse of the square root of the number of RV (patients #p, listed in Table 1). The SD of the estimated Improvement Factors IF in Table 2 is resulting from error propagation calculus.

Conclusion

Up to now there is no sufficient and convincing explanation for the striking discrepancies between the leading publications in 2009 and 2017 by a factor of about 2.5 with respect to the virtual improvement of mortality rates for different stages of melanoma disease. Therefore it seems necessary that this issue should be taken seriously and as a matter of revision and re-evaluation and further investigation.

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