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Does Statistical Decrease of Mortality Rates by a Factor of about 2.5 Suggest Revolutional Progress in Melanoma Treatment from Year 2009 to 2017?

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Abstract

Comparison of mortality rates (for 5 years and 10 years, resp.), derived from the leading AJCC melanoma staging system references from 2009 and 2017, are showing an astounding decrease by a factor of about 2.5 (± 0.1) for different cutaneous melanoma stages, e.g. IIB, IIC, and IIIB, whereas the respective comparison between the former references from 2001 and 2009 amounts only to a factor of about 1.1 (± 0.05). The dramatic improvement in the short time from 2009 to 2017 suggests a revolutional progress in melanoma treatment, perhaps unsurpassed in the history of cancer.

Background

Comparison of mortality rates (for 5 years and 10 years, resp.), derived from the leading AJCC melanoma staging system references from 2009 and 2017 [1], are showing an astounding decrease by a factor of about 2.5 (± 0.1) for different cutaneous melanoma stages, e.g. IIB, IIC, and IIIB, whereas the respective comparison between the former references from 2001 and 2009 amounts only to a factor of about 1.1 (± 0.05).

The dramatic improvement in the short time from 2009 to 2017 suggests a revolutional progress in melanoma treatment, perhaps unsurpassed in the history of cancer.

However, this striking phenomenon lacks convincing explanation up to now. Neither Thesis 1, misclassification in former patient data, nor Thesis 2, the impact of novel therapies, can be sufficiently validated.

Therefore it seems important that the issue should be taken seriously as a matter of revision and re-evaluation and deeper investigation.

Material and Method

As material for the present study data from the leading publications in 2001 and 2009 by Balch et al. [1,2] and in 2017 by Gershenwald et al. are used [3].

In order to elucidate the discrepancies between the 2017 and the 2009 papers [3] and [2], it makes sense to replace empirical "survival rates" p_s by "mortality rates": p_d=1-p_s.

For example: An improvement of survival rate from 0.90 to 0.95 looks small, however complementary mortality rates from 0.10 to 0.05 signify that the number of mortalities is halved, which means a large progress. Moreover: mortality and metastatic recurrence are "positive" *events*, survival is not. In Table 1 the 5 years *survival rates* for stages IIB, IIC, IIIB and for node categories N1a, N1b, N2a, N2b resp. 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) as the quotients of the mortality rates from 2001 and 2009 (4th column) and the data from 2009 and 2017 (5th column) respectively. Stage IIIC and node subcategories N2c and N3 are 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 and node sub-categories are affected as little as possible, if that, by the redefinitions in 2017. A further criterion chosen was that the 5 years overall survival is smaller or less than 70 % (in the 2009 publication).

Results

The data from 2009 and 2001 seem to be consistent in that the survival and mortality rate

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Table 1: Overall survival rate within 5 yrs/% according to AJCC publication. The values in third row are read from survival curves in Figure 1 in [2], reading error is 1% to 2%.

Melanoma Category	overall **survival** rate within **5 yrs** / % according to AJCC publication		
	[1] (2001)	[2] (2009)	[3] (2017)
Stage			
II B	**67**	**69**	**87**
II C=T4b	**45**	**53**	**82**
III B	**53**	**58**	**83**
N-category			
N1a		70	84
N1b		48	76
N2a		60	79
N2b		44	71

Table 2: Mortality rate within 5 yrs/% according to AJCC publication, the numbers in the right-most columns are rounded to the nearest digit.

Melanoma category	**Mortality** rate within **5 yrs**/% according to AJCC publication			Improvement (2001)/(2009)	Improvement (2009)/(2017)
	[1] (2001)	[2] (2009)	[3] (2017)		
Stage					
II B	**33**	**31**	**13**	1.07	**2.4**
II C = T4b	**55**	**47**	**18**	1.17	**2.6**
III B	**47**	**42**	**17**	1.12	**2.5**
N-category					
N1a		30	16		1.9
N1b		52	24		2.2
N2a		40	21		1.9
N2b		56	29		1.9

data are of similar magnitude and the data from 2009 are showing a slight improvement by a factor of about 1.1 (± 0.05) with respect to the data from 2001. However, from 2009 to 2017 a virtually huge improvement by a factor of about 2.5 (± 0.1) is showing up for the stages IIB, IIC, IIIB both for the 5 years mortality rates and the 10 years ones (not tabulated) (Table 2). Formal evaluations for stages IA, IB, IIA, IIIA for the 5 years mortality rates resulted also in high virtual improvement factors, ranging between 2.5 and 3.3 (not tabulated). The improvement factors for the node categories N1a, N1b, N2a, N2b, resp. are ranging between 1.9 and 2.2 for the 5 years mortality rates (Table 2), and the 10 years relations between 1.7 and 2.5 (not tabulated). As a general result can be stated a *virtual improvement factor of about* 2 (ranging from 1.7 to 2.6) of mortality rates from the standard publications in 2009 and 2017 throughout melanoma stages IIB, IIC, IIIB and node categories N1a up to N2b.

Discussion

This striking phenomenon lacks convincing explanation up to now. In some possible factors are mentioned, such as miss-classification in the 2009 data or introduction of novel efficient therapy methods (such as checkpoint inhibitors) [3], which might partly explain the dramatic reduction in mortality rates. In the following the two theses and their combination will be tested:

Thesis 1

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

Counter-validation: Let us take as example stage IIC and 5 years mortality rates from 2017 data for granted. Let us assume that part of the IIC classifications in 2009 should have been in fact IIID (a new category of bad prognosis, introduced in 2017).

Question: what portion x of misclassifications could explain the high mortality rate of 0.47 in the 2009 paper?

Answer: The corresponding mortality rates in the 2017 paper are 0.18 for stage IIC and 0.68 for stage IIID.

Thus the following equation for the unknown portion x of misclassifications reads:

$0.47=(1-x)0.18+x0.68;$

from this follows: $x=0.58$

If one takes the 10 years mortality rates, then the result is $x'=0.7$.

Consequence: in order to "explain" the huge virtual "improvement" from 2009 to 2017 by thesis 1, it must be assumed that much more than half of the diagnostic stagings in 2009 have been false, i.e. most multi-node infiltrations have been missed. Surely, nobody would accept such poor state of the art of oncological diagnostics. Therefore thesis 1 fails as a convincing explanation.

Thesis 2

Use of novel highly efficient therapies, such as based on checkpoint inhibitors, might explain the decrease of mortality rates.

Counter-validation: Let us take again for example stage IIC in Table 2. The 5 years mortality rates are 0.47 based on the 2009 paper and 0.18 on the 2017 one. Let's optimistically assume that half of the patients in 2009 be treated by the novel therapies for which 60% complete response might be attained. On the other side the 40% non-responders' mortality rate will be unchanged. These assumptions will result in an updated mortality rate of $(0.5+0.5 \times 0.4) \times 0.47=0.7 \times 0.47=0.329$. This is far away from 0.18 by a factor of 1.83. The other examples, i.e. stages IIB and IIIB and/or 10 years mortality rates, give similar results. Furthermore, the impact on 10 years mortality rates are expected to turn out much smaller, because the novel therapies have not yet been applied long enough. Therefore also thesis 2 fails.

Note

In a recent publication a randomized, placebo-controlled phase 3 trial using Ipilimumab as adjuvant therapy in patients with resected stage III melanoma is reported [4]. 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 mortality rates the improvement by Ipilimumab therapy *vs.* placebo was by a factor of 1.3. This is also far away from factors about 2 or 2.5, resulted from the 2009 *vs.* 2017 comparison.

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 (or more) with respect to the virtual improvement of mortality rates for different stages and categories 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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