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Editorial

Embracing changes to the American Joint Committee on Cancer 8th edition melanoma staging system

Melanoma staging represents an essential communication tool between physicians and their patients, and informs prognostic assessment and clinical decision-making [1]. It is used for clinical trial design, eligibility, stratification and analysis and is foundational for reporting in institutional, state, national and international data registries. The American Joint Committee on Cancer (AJCC) staging system is revised periodically as new information relevant to staging becomes available for each tumour type. The most recent (8th edition) of the AJCC Cancer Staging Manual was published in 2017 [2] and implemented worldwide in 2018. For the cutaneous melanoma chapter, several significant changes were made following analysis of a large new international melanoma database supplemented by analyses from the legacy 7th edition AJCC stage IV database and by data from contemporary clinical trials [3].

Despite the advantages of using a staging system based on more contemporary outcomes data, it was suggested by Grob et al [4] in a 2018 opinion piece that the AJCC melanoma staging system should not have been revised to produce the current 8th edition, recommending instead that it be ignored and that the 7th edition melanoma staging system, implemented in 2010, continue to be used for patients presenting with regional metastasis (stage III melanoma). The stated reasons for this viewpoint included speculation that the 8th edition 'will create significant confusion in clinical practice' and the opinion that a staging system should remain stable, will only be used if it does not change very often and only requires updating 'when completely new biomarkers are validated that significantly improve clinical decision-making'. However, an ostensibly key underlying rationale for the authors' general reluctance to embrace change is that they considered it impractical to 'map' or convert the 8th edition stage groups to corresponding 7th edition stage groups, presumably to allow uniformity of staging for clinical trial purposes.

The authors acknowledged that the 8th edition AJCC melanoma staging system is 'very relevant' for stage IV melanoma and 'better reflects the current evolution of the management of primary melanoma' for stages I and II, underscored by the improved staging and prognostic assessment made possible by the use of a newly created database of >46,000 patients with stage I-III melanoma diagnosed in the contemporary era (since 1998, when lymphatic mapping and sentinel lymph node [SLN] biopsy had become a routine part of the staging workup of patients with melanoma in most melanoma centres worldwide). Notably, survival analyses required SLN biopsy for clinically node-negative patients with T2-T4 primary melanomas, and SLN biopsy information was used for patients with T1 melanoma who had SLN biopsy as a component of their initial surgical treatment. In contrast, data used for the 7th edition included large numbers of patients diagnosed from the 1960s to the early 1990s, a period when this important staging procedure was not performed. Hence, many of the patients included in the 7th edition analyses and classified as having stage I or II melanoma would undoubtedly have harboured clinically occult nodal metastases (i.e., tumour-involved SLNs), resulting in inaccurate staging because they in fact had stage III disease.

Predictably, as a consequence of understaging of some patients in both the 7th edition cohort and the more robust 8th edition stage III subgroups, resulting from formal inclusion of T-category criteria, the prognosis for many patients with stage III melanoma in the 8th edition analyses is substantially better (93%, 83% and 69% 5-yr survival for stage IIIA, IIIB and IIIC, respectively [5]) than in the 7th edition (78%, 59% and

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40% 5-yr survival for stage IIIA, IIIB and IIIC, respectively [6]). The proposal of Grob *et al.* [4] to continue staging patients based on the 7th edition would inevitably have the consequence of providing less reliable estimates of patient outcome, by not reflecting the outcome of patients treated in a more contemporary era.

Furthermore, the concern expressed in relation to clinical trials is spurious. Any clinical trial currently under way, for example, will continue to enrol and stratify patients and collect data according to the staging system and trial schema detailed in the active trial protocol. Conversion of patient staging to a new version of the staging system for ongoing clinical trials when implemented has not been a standard approach following prior revisions of the melanoma staging system but is easily possible. It was performed, for example, for the COMBI-AD trial of adjuvant dabrafenib and trametinib for patients with resected BRAF V600-mutant stage III melanoma [7]. Moreover, presented at the 2018 Society for Melanoma Research Congress, *post hoc* analysis of KEYNOTE-054, a randomised trial of adjuvant pembrolizumab versus placebo in patients with high-risk resected melanoma, demonstrated that conversion of the trial data into AJCC 8th edition stage groups was possible and prognostic significance was maintained [8]. As the discrete data elements required for initial stage assignment did not change appreciably from the 7th to the 8th edition (with the minor exception that mitotic rate is no longer included as a T1 subcategory criterion), no additional data element collection effort for the purpose of calculating stage group is even required, as all required staging elements (i.e., tumour thickness, ulceration, regional node and non-nodal regional factors) would already be captured for either system. If such individual data elements are not collected and only the summary stage group values are known, it would indeed not always be possible to convert to the 8th edition. However, in general, this latter scenario does not reflect best practice for data collection because the quality of the recorded stage groups would not be verifiable. Thus, the problem foreseen by Grob *et al.* [4] is related to deficiencies in data recording, not that a new staging system was created and implemented.

It is somewhat bewildering that the authors referenced 'The survival curves for AJCC 8th version in stage IV melanoma …' and 'The more prognostically accurate relapse-free survival (RFS) curves in stage IIIA-D in the 8th AJCC version …' in their article as these analyses have not yet been published. This calls into question the thoroughness of their assessment of the 8th edition AJCC staging system and may explain how they have reached sometimes incorrect conclusions. As clearly stated in the AJCC Cancer Staging Manual [3] and related publications [1,5], owing to the complexity of outcomes in the stage IV melanoma setting with myriad new immune and targeted systemic treatments, contemporary stage IV patient outcomes were neither collected nor analysed for the 8th edition. Indeed, as the general charge to revise staging criteria has been based on overall or disease-specific survival across essentially all tumours since inception of the AJCC Cancer Staging Manual, melanoma relapse data has not yet been formally collected nor analysed for any melanoma cohort specifically used to inform any edition of the AJCC staging system, including the 8th edition. From a conceptual perspective, we completely concur that such information is likely to be useful; to this end, the International Melanoma Database and Discovery Platform (IMDDP) working group is embarking on a second phase of expanded, international data collection and analysis, including assessment of RFS outcomes, an area of work we agree is an important next step.

Of significant concern is the recommendation by Grob *et al.* that the 8th edition staging system for stage III melanoma should be abandoned and 7th edition staging maintained. This unprecedented and curious recommendation for using less accurate survival estimates will not only provide patients with inaccurate information but may also take the field backwards by basing the evaluation of future treatment protocols on a benchmark derived from outdated clinical data. It also has the potential to cause significant confusion in the global melanoma clinical and scientific community (the very issue that the authors claim they seek to avoid).

It is evident that stage III melanoma clinical decision-making and patient management will be improved by the use of the contemporary, 8th edition, melanoma-specific survival estimates. The melanoma treatment landscape continues to evolve rapidly, with an ongoing paradigm shift in surgical, adjuvant and neo-adjuvant treatments. It is essential that we establish and subsequently evaluate these changes in treatment on the basis of accurate survival estimates. The notion that the evolution of clinical care away from completion of lymph node dissection for patients with a positive SLN will have an important impact on staging is conceptually accurate, although the magnitude of this impact is likely far more limited than might initially be surmised. With the addition of tumour thickness as a component of 8th edition stage III stage groups, the *minimum* stage III substage for patients with 1−3 positive SLNs whose primary melanoma is categorised as T2b through T4b would be *at least* IIIB. With a 5-year melanoma-specific survival for patients with stage IIIB melanoma of 83%, there is near-uniform consensus among melanoma clinical experts that patients with stage IIIB, IIIC or IIID melanoma should be offered adjuvant therapy. From another perspective, the decision-making challenge regarding whether a patient with a positive SLN would be offered adjuvant therapy is in practical terms limited to patients with 8th edition stage IIIA melanoma. Based on studies to date that have sought to establish predictive models related to the likelihood of

tumour involvement of non-sentinel nodes, most patients with T1a/T1b/T2a melanoma (that in part define 8th edition stage IIIA) would be estimated to have an approximately *5% or less* risk of harbouring positive non-SLNs [9]. Nonetheless, we are in complete agreement with Grob *et al.* that this is a clinically relevant matter and the AJCC Melanoma Expert Panel has already mobilised the IMDDP consortium to explore this important theme, aiming to inform the melanoma community as these analyses mature.

We agree with the authors that for patients with melanoma, 'we are now in a crucial period in the management of stage III disease with the introduction of new and effective targeted and immune strategies in the adjuvant setting' and also agree that it is essential to appreciate the real benefits of these new strategies. We acknowledge the kind words by Grob *et al.* regarding the outstanding work conducted by the AJCC Melanoma Expert Panel and look forward to ongoing and future opportunities to continue the process of developing and implementing contemporary validated clinical tools, including the integration of new biomarkers. Our goal is to progressively refine melanoma staging and classification, to facilitate further improvements in clinical decision-making and to contribute to the design and success of future clinical trials.

Conflict of interest statement

J.F.T. has been a member of advisory boards for and received honoraria/travel support from GlaxoSmithKline, Merck Sharp Dohme, Bristol-Myers Squibb and Provectus Inc, all unrelated to the content of this work. J.E.G. has served in a consultant or advisory role for Merck, Bristol-Myers Squibb, Novartis, Syndax, Neracare and Castle Biosciences, unrelated to the content of this work. R.A.S. has served on advisory boards for Merck Sharp Dohme, Novartis, Myriad and NeraCare, unrelated to the content of this work. L.E.H. has no potential conflicts to disclose.

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