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COMMENTARY

Progress but not enough: the 2009 (7th) revision of the American Joint Committee on Cancer (*AJCC*) for melanoma staging and classification

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Summary

In 2009 the American Joint Committee on Cancer (AJCC) examined for the first time the mitotic rate of the primary melanoma as a new covariate in a revised staging and classification system. In a multifactorial analysis mitotic rate was the second most powerful predictor of survival after tumour thickness, reaffirming the findings of earlier studies. Analyses demonstrated a highly significant correlation between increasing mitotic rate and declining survival rates. Despite these findings some of the intrinsic weaknesses of the 2001 staging and classification system for melanoma remain apparent in the 7th revision of 2009 and are discussed in this paper.

Introduction

In 2001, the Melanoma Staging Committee of the *AJCC* proposed major revisions of the tumour-node-metastasis (TNM) categories and stage grouping criteria for cutaneous melanoma and proffered the 6th version of a new staging system [1,2]. The dominant recommendation among these proposals was that the thickness as well as the presence of ulceration of the primary lesion –as determined by microscopic histopathologic examination– should be used in the tumour (T) classification [2]. There is no naturally occurring cut-off point for the thickness of primary melanoma that delineates defined risks of mortality from the neoplasm. Consequently, an improvement of the 2001 staging system was the introduction of even integers for the thresholds of the tumour thickness rather than the previously employed threshold of 0.75 mm between T1 and T2 tumours [2].

The second important improvement was in the N category with the introduction –after years of confusion in the literature– of the crucial distinction in prognosis between clinically occult and clinically apparent regional lymph node metastases [2,3].

A critical appraisal of the 2001 staging system was presented in 2007, with the imperative proposal, among others, for incorporation of the mitotic rate of the primary lesion (/mm^2) in the tumour classification [3] in the next revision of the *AJCC* staging for melanoma; an important prognostic factor, second only to tumour thickness, determining overall survival as shown in numerous studies since the 1970's [4-6].

The 2009 (7th) Revision

The *AJCC* committee made their recommendations in the 2009 version based on findings of multivariate analyses of data from an expanded database of 30,946 patients with stages I, II, and III melanoma and of 7,972 patients with stage IV disease [7].

The 2009 revised staging and classification system examined for the first time mitotic rate of the primary melanoma as a new covariate [7]. In a multifactorial analysis of 10,233 patients with clinically localised melanoma, mitotic rate was the second most powerful predictor of survival, after tumour thickness (x^2 =79.1; $p \leq 0.0001$) reaffirming the findings of earlier studies [4-6]. Although analyses demonstrated a highly significant correlation between increasing mitotic rate and declining survival rates the Committee elected to utilise this powerful prognostic factor only in the classification of the T1a & T1b categories making no use of its importance in the remainder of the T classification

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(categories T2-T4) or indeed in addressing the staging for regional lymph node metastases [7].

The authors of the revision state that survival times were calculated from the initial diagnosis (or first distant metastasis for the stage IV analysis) but no reference is made to the calculation of survival times for clinically apparent regional lymph node metastases – admittedly in a minority of patients in the *AJCC* database– which however can be present at initial diagnosis or may appear many years later [3,8,9].

In the staging for distant metastases (stage IV disease) the *AJCC* committee retained the prognostic value of lactate dehydrogenase (LDH) but once again did not give consideration to serum S100β protein, a tumour marker commonly used in Europe with higher specificity and sensitivity for melanoma than LDH [3, 10-12]. In one study the combined raised levels of serum LDH and S100β predicted a particularly poor survival from stage IV melanoma [13].

Taking these facts into consideration the intrinsic weaknesses of the 2001 staging system [3] remain apparent in the seventh, 2009 version. An example of this –as already noted by others [14]– is the survival of patients with stage IIIA disease which in the *AJCC* 2009 revision document (Figures 1B & 1D) [7] appears better than the survival of patients with stage IIB and IIC disease!

Despite a very large database and the recognition of the prognostic significance of mitotic rate of the primary lesion –second only to tumour thickness– the *AJCC* Committee did not address the predictive power of the combined histopathologic characteristics of the primary lesion (algorithm), in relation to the metastatic status of the regional lymph nodes.

This essential task was undertaken recently by a British study with a considerably smaller database which nevertheless provides the first evidence that prognosis can be better predicted if clinicians used combined data from the pathology report of the primary tumour in a model, rather than using the Sentinel Node Biopsy (SNB) result [15]. The confirmation of this concept from additional studies is awaited with interest.

The inherent flaws of the 2001 staging system as discussed previously [3] remain apparent in the 2009 revision perhaps because the authors elected to give priority to the surgical staging of metastatic nodal involvement (SNB) –a procedure that confers no added protection to the patient [16]– rather than to the optimal use of the naturally occurring prognostic factors of the primary lesion such as the mitotic rate. The latter are easier to evaluate, require less labour and expense and do not add morbidity to the patient. They deserve the full attention of pathologists and clinicians involved in the management of melanoma.

References

1. Balch CM, Soong SJ, Gershenwald JE et al. Prognostic factors analysis of 17,600 melanoma patients: Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 2001; 19: 3622-3634.
2. Balch CM, Buzaid AC, Soong SJ et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 2001; 19: 3635-3648.
3. Retsas S, Mastrangelo MJ. Reflecting on the 2001 American Joint Committee on Cancer Staging System for Melanoma. Semin Oncol 2007; 34: 491-497.
4. McGovern VJ, Shaw HM, Milton GW et al. Prognostic significance of the histological features of malignant melanoma. Histopathology 1979; 3: 385-393.
5. Retsas S, Henry K, Mohammed MQ et al. Prognostic factors of cutaneous melanoma and a new staging system proposed by the American Joint Committee on Cancer (AJCC): Validation in a cohort of 1284 patients. Eur J Cancer 2002; 38: 511-516.
6. Azzola MF, Shaw HM, Thompson JF et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: an analysis of 3661 patients from a single centre. Cancer 2003; 97: 1488-1498.
7. Balch CM, Gershenwald JE, Soong Seng-J et al. Final Version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 2009; 27: 6199-6206.
8. Berd D, Mastrangelo MJ, Sato T. Calculation of survival of patients with stage III melanoma. J Clin Oncol 2005; 23: 9427.
9. Retsas S, Quigley M, Pectasides D et al. Clinical and histologic involvement of regional lymph nodes in malignant melanoma. Adjuvant vindesine improves survival. Cancer 1994; 73: 2119-2130.
10. Guo HB, Stoffel-Wagner B, Bierwirth T et al. Clinical significance of serum S100 in metastatic malignant melanoma. Eur J Cancer 1995; 31A: 924-928.
11. Hauschild A, Michaelsen J, Brenner W et al. Prognostic significance of serum S100B detection compared with routine blood parameters in advanced metastatic melanoma patients. Melanoma Res 1999; 9: 155-161.
12. Martenson ED, Hansson LO, Nilsson B et al. Serum S-100b protein as a prognostic marker in malignant cutaneous melanoma. J Clin Oncol 2001; 19: 824-831.
13. Mohammed MQ, Abraha HD, Sherwood RA, MacRae K, Retsas S. Serum S100beta protein as a marker of disease activity in patients with malignant melanoma. Med Oncol 2001; 18: 109-120.
14. Thomas JM, Strauss DC, Hayes AJ. Some of the 2009 American Joint Committee on Cancer Melanoma Staging and Classification Is Not Evidence Based. J Clin Oncol 2010; 28: p e479.
15. Mitra A, Conway C, Walker C et al. Melanoma sentinel node biopsy and prediction models for relapse and overall survival. Br J Cancer 2010; 103: 1229-1236.
16. Retsas S. Sentinel node biopsy confers no added protection to patients with melanoma. J R Soc Med 2007; 100: 391-392.