Clinical relevance of melanoma micrometastases in sentinel nodes: too early to tell

We read with great interest the recent article by Dr van Akkooi and colleagues reporting the results of their study of 74 patients with sentinel nodes (SNs) containing metastatic melanoma but have great concern about the authors’ conclusions regarding the clinical significance and clinical relevance of tiny SN metastases [1]. The authors sought to identify patient/tumor and/or SN factors that predicted additional non-SN positivity as well as disease-free survival (DFS) and overall survival (OS). The microanatomic features of the SNs that were assessed included the intranodal location of the SN metastases (using the classification scheme of Dewar et al. [2]), the tumor penetrative depth of the deposits (Starz classification) [3, 4] and the ‘amount of SN tumor burden’ [1]. No additional non-SN positivity was found in 15 patients with SN micrometastases <0.1 mm (although this was not statistically significant compared with their other tumor burden categories). On multivariate analysis, SN tumor burden was the most important prognostic factor for DFS (P = 0.005) and OS (P = 0.03). No association between the microanatomic location of SN metastases or Starz thickness and non-SN positivity, DFS or OS was found. On the basis of their results, they concluded that patients with melanoma SN metastases <0.1 mm “may be judged as SN negative … and are highly unlikely to benefit from completion lymph node dissection (CLND), which we no longer recommend” [1].

Consistent with the results of a number of other recent studies [2–13], the findings of van Akkooi et al. support the concept of orderly progression of lymph node melanoma metastases whereby the risk of tumor spread from SNs to non-SNs correlates mostly with the extent of SN involvement. However, it is disappointing that the association of certain SN tumor burden parameters (such as Starz’ centripetal thickness i.e. tumor penetrative depth of the deposits, the microanatomic location of SN tumor deposits and the size of metastases in the SN) with non-SN positivity and survival reported in some studies are not being reproduced in others [2–14]. We believe that there are
two principal reasons for this that are not fully addressed in the article by van Akkooi et al. and require further comment.

First, most of the studies reported to date have used different sectioning/staining protocols for pathologic analysis of SNs and non-SNs. This may have an effect not only on the detection of melanoma metastases in SNs and non-SNs but also on the assessment of the size and location of small metastatic deposits in SNs. For example, a few extra levels cut from a SN may reveal that a very small deposit (say <0.1 mm in the subcapsular sinus) is in fact much larger and extends into the parenchyma of the SN.

The second and perhaps more important factor that causes a lack of concordance between results from different centers is the difficulty in classifying/measuring/assessing parameters. van Akkooi et al. do not mention whether they encountered any interpretative problems when performing their microanatomic analyses of SNs. In theory, particularly to those who have not attempted it, each of the studied micromorphometric features should be easy to measure. However, in our experience of reviewing many SNs and attempting to measure these parameters, this is often not the case. For example, metastatic deposits are usually not spherical, making measurements of their size problematic without the aid of specialized equipment [8]. For small deposits it can be difficult to determine the edges of individual deposits, as a few dissociated cells may be present at the periphery. Similarly, it is often open to interpretation when metastatic deposits in the subcapsular sinus extend into the parenchyma of the lymph node because there is no definite microanatomic landmark that separates these compartments within a lymph node when examined under the microscope.

We have encountered other difficulties when attempting to determine Starz’ centripetal thickness of metastatic deposits if the lymph node is lobulated (a common occurrence), if the deposit is towards the medulla of the SN (where the capsule is usually deficient) or if the deposit involves more than one half of the SN [7]. Interobserver reproducibility of assessment of micromorphometric parameters of metastatic deposits has not been reported in any of the studies published to date and requires further investigation.

We have great concern about the authors’ conclusion that ‘patients with submicrometastases (<0.1 mm) in the SN may be judged as SN negative … and are highly unlikely to benefit from CLND’ [1]. As the study was retrospective with all melanoma patients with a positive SN having a CLND, the authors appear to have discounted the possibility that a therapeutic benefit may have been afforded their patients as a result of the SN biopsy itself and/or the CLND. While it is possible that CLND may not be necessary in all patients with a positive SN, patients with tiny SN metastases still had the minimal disease identified by removal of their SNs in the first place replacing the possibility that even removal of the SN may have impacted upon survival. Recently published results of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I) indicate that there is a benefit to performing a CLND in patients with a positive SN, at least in those with with primary melanomas 1.2–3.5 mm in thickness [15].

Another significant potential confounding factor in the study by van Akkooi et al. (which had a median follow-up period of only 30 months) is lead time bias, whereby the smaller the metastatic deposit the longer it will take for recurrence of the disease to be detected and death to occur. Evidence contrary to the view that all melanoma patients with small metastatic deposits can be ‘judged as SN negative … and are unlikely to benefit from CLND’ [1] comes from review of patients with false-negative SNs. We have identified a small number of melanoma patients whose SNs were originally reported as pathologically negative but have subsequently developed disease recurrence in the same regional node field; subsequent more detailed pathologic analysis revealed very small (‘sub-micrometastatic’) deposits in the subcapsular sinus region of the SN [16, 17]. Furthermore, recently reported follow-up evidence from MSLT-I indicates that patients with a false-negative SN biopsy had a worse survival than those with true-negative SNs [15].

Further studies are necessary to optimally define the most accurate and practical method of identifying patients with a low probability of having metastatic tumor in non-SNs, in order to select patients who can be spared a CLND. In addition, clear and precise definitions of terms, reliable interobserver reproducibility and ease of assessment of histologic parameters will be required if micromorphometric features of tumor within SNs are to be useful as predictors of prognosis and possible determinants of patient management. Detailed measurements of tumor burden within SNs are being made in the second MSLT (MSLT-II), the results of which may determine the clinical significance and clinical relevance of tiny SN micrometastases and identify which patients with a positive SN may safely be spared a CLND.

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