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Isolated Tumor Cells and Long-Term Prognosis of Patients with Melanoma

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To the Editor:

Sheri et al. reported in the *Annals of Surgical Oncology* on the significance of isolated tumor cells (ITC).[1] At the moment the subject of ITC or SUB-micrometastases, minimal sentinel node (SN) tumor burden is a hot issue. Therefore, it is very interesting that the experience from the John Wayne Cancer Institute (JWCI) has been reported. This recent publication does raise a few questions with regard to the different results acquired by the authors compared with recent publications by others.[2,3]

The first point of note is that the experience from the JWCI goes back to 1991; this is an advantage, because this leads to a longer median follow-up compared with other single-center studies.[2,3] However, at the same time, it means that patients from the early days of SN staging have been included. This is a drawback because the pathology protocol, which nowadays includes bivalving through the hilum, more step-sections, more immunostains, and smaller intervals,[4,5] was less extensive in the early days of SN staging. This may be reflected in the very low SN positivity identification rate of only 15%, compared with many other studies, which report rates between 20% and 30%.[5,6]

This is supported by the fact that the authors have found additional positive nodes in the completion lymph node dissection (CLND) in 6 of 52 patients (12%) with ITC. An extensive "modern" pathology protocol should probably have picked up larger tumor lesions in the original SN. We wonder if the authors have extended the workup of the SNs of these six patients to meet the standard extensive workup used nowadays?

The second point of note is the extremely good survival of SN negative patients reported by the authors of 94% at 5y ears. This is somewhat higher than in most other series, including the MSLT-I trial, which report rates of around 90%.[6,7] The reason for this is that the SN negative patients had a much smaller median Breslow thickness (1.2mm!) compared with the MSLT-I trial (1.8mm) or other series.[5,7]

The authors report that even if ITC would have implications, its occurrence is very low at only 4%. However, shouldn't this rate be calculated as proportion of all SN *positive* patients? This is 57/214 = 27%, who could possibly *not* benefit from CLND in our experience.

We believe that isolated tumor cells are not always important, as has recently been demonstrated in a multicenter trial for the detection of isolated tumor cells using polymerase chain reaction (PCR) techniques. Scoggins et al. did not demonstrate additional prognostic information beyond standard hematoxylin-eosin (HE) staining of SNs.[8] Although Scheri et al. demonstrate a decreased survival in their group of patients with ITC defined as <0.2mm,[1] we believe that the prognosis of patients with SUB-micrometastatic disease as defined as <0.1mm has no impact on overall survival. A multicenter study conducted within the EORTC

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Melanoma Group and recently presented at ECCO 14 in Barcelona, showed that patients with <0.1mm SUB-micrometastases had an excellent 5-year overall survival rate of 91%. The rate of additional non-SN positivity in CLND was 3% (which is identical to the false negative rate in the MSLT-1 trial).[9] We have also addressed the limit of 0.2mm as definition for SUB-microscopic disease. The overall survival decreased slightly to 89% at 5y ears; however the occurrence of CLND positivity increases significantly to 10%, which leads us to believe that melanoma and breast cancer have a different biology and thus require different cut-off values for SUB-micrometastases.

Whether the excellent survival of patients with <0.1mm SUB-micrometastatic disease is achieved because of or in spite of CLND remains to be seen and is the subject of an EORTC Melanoma Group registration study, the MINITUB, which shall be activated within the next year. Perhaps the MSLT-II trial will also answer the question of which group(s) of SN patients may or may not benefit from CLND. Until more data are available, clinicians should realize that advising removal of all regional nodes to all of their patients might change with respect to further insights in long-term behavior of SUB-micrometastatic involvement of the SN.

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