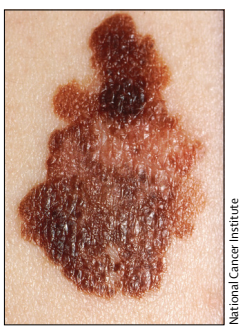
Excision margins for melanomas: how wide is enough?



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The main aim of surgery in treating any cancer is to completely excise the tumour, thereby preventing local recurrence. In the case of melanoma, the purpose of a wide excision is to remove local micrometastases and otherwise phenotypically normal tissue that might be harbouring genotypically abnormal cells located in either the surrounding cutis or superficial lymphatics, while at the same time trying to prevent unacceptable functional and cosmetic harm to the patient as a result.

In *The Lancet Oncology*, Andrew Hayes and colleagues[1] report the long term follow-up data from the UK excision margins trial,[4] which started in 1993. The original work has been included in meta-analyses, and the data have been key in producing international guidance on the surgical management of melanoma. The latest analysis of the data[1] suggests that the narrower excision margin of 1 cm is associated with worse disease-specific survival, estimated as an absolute difference of 5·95% (95% CI –0·54 to 12·44) at 10 years, compared with that in patients who had the wider 3 cm excision margin at a median follow-up of 8·8 years: (unadjusted hazard ratio [HR] 1·24 [95% CI 1·01–1·53], p=0·041).

These data are important because they seem to contrast with findings from five other randomised trials suggesting that narrow margins around melanomas (1 cm or 2 cm) are just as safe as wide ones (3 cm, 4 cm, or 5 cm).[2] Currently, only the UK national guidelines[3] continue to recommend 3 cm margins around thicker primary melanomas, compared with guidelines from other countries that recommend 2 cm as the maximum margin. Hayes and colleagues propose that the findings in their long-term analysis are linked directly to their previous finding of increased locoregional recurrence associated with the narrower 1 cm excision margin compared with the 3 cm excision margin.[4] However, in both surgical groups, the incidence of nodal recurrence outweighed the incidence of local recurrence by at least 5 to 1. In view of the findings of the MSLT-1 study,[5] in which the incidence of sentinel node positivity matched the number of nodal recurrences, especially for thick melanomas, most of these nodal metastases would probably have been detected by sentinel-node biopsy, if it had been done at the time of the intervention. Accordingly, a plausible alternative explanation is that the excess nodal disease in the narrow margin group was indicative of poor prognostic disease before the intervention, rather than resulting from the narrow margin intervention itself.

The overall recurrence data, including data for in-transit metastases, from the primary analysis[4] were remarkably similar between the 1 cm and 3 cm groups (5·7% *vs* 4·7%). However, when analysed as a specific secondary endpoint, the difference in local recurrence between the groups was greater, although not significantly (8·2% *vs* 5·6%; HR 1·51 [95% CI 0·91–2·51]; p=0·1).[4] Since 2004, it has become clear that the presence of microsatellites—representing microscopic, discontiguous, intralymphatic extensions of melanoma directly adjacent to the primary tumour—is a poor prognostic indicator for melanoma, and is now classified as stage III disease.[6] Whether an excess of microsatellites was present in the 1 cm group before or at randomisation in the present study is unclear, because this information was not included in the standard synoptic report at the time. Nevertheless, the evidence could be signalling that the 1 cm excision margin might be inadequate to deal with microsatellites in particular. Data from the recent Scandinavian wide excision trial[7] is consistent with this notion, because local recurrence was higher in the narrow margin group (2 cm) than in the wide margin group (4 cm), although this was not significant. Data from a large, retrospective study investigating risk factors for locoregional recurrences[8] have suggested that in-transit metastases and local recurrences are associated with an increased incidence of subsequent regional nodal relapse, despite an initially negative sentinel node.

In summary, the implication of Hayes and colleagues' study is that high-risk melanoma phenotypes might be unmasked by a narrower, 1 cm wide-excision margin around tumours and these risks could manifest as clinically detectable local or regional recurrences (or both) in follow-up. Closer inspection of the data, however, suggests that this subgroup of patients is small and that most patients could be safely managed without creating 4–6 cm wide excision defects. A multinational, phase 3 clinical trial in progress aims to confirm this (NCT02385214). Accordingly, clinicians' efforts might

be supported by the identification of biomarkers to recognise the high-risk minority of patients, especially those with a microscopic locoregional extension at the time of diagnosis of their primary melanoma. These patients might benefit from a wider, elective excision margin for their melanoma, or indeed, adjuvant therapies that might become the standard of care in the near future.

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I declare no competing interests.

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Cancer screening after unprovoked venous thrombosis

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The risk of an underlying malignant disease is increased in patients presenting with unprovoked venous thromboembolism, particularly with increasing age, with an estimated prevalence of hidden cancer of around 10%.[1,2] Although, at least theoretically, workup for occult cancer in this scenario could lead to early diagnosis and reduce cancer-related mortality, this hypothesis has not yet been confirmed.[3] Indeed, conducting a randomised trial on this topic is not an easy task, because there are plenty of methodological difficulties to face.

The recently published SOME study[4] concluded that, in patients with unprovoked venous thromboembolism, routine screening with comprehensive CT of the abdomen and pelvis (including virtual gastroscopy and colonoscopy) did not provide a clinical benefit when added to a limited workup, which included complete history taking and physical examination, complete blood counts, liver and kidney function tests, chest radiography, mammography (for women older than 50 years), Pap smear testing (for women 18–70 years of age who had ever been sexually active), and prostate-specific antigen test (for men older than 40 years). The limited strategy missed four of 14 cancers diagnosed during the 1 year follow-up period, compared with five of 19 cancers with the extensive strategy. These results, together with other previous studies, have—for now—cooled the enthusiasm for cancer screening in patients with venous thrombosis.[5,6]

But when a door closes, another opens. In *The Lancet Oncology*, Philippe Robin and colleagues[7] reignite the debate with the results of the first randomised trial comparing a limited screening strategy with the limited strategy plus ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT for cancer screening in patients with unprovoked venous thromboembolism. ^{18}F-FDG PET/CT seems an attractive tool to this aim because it is a non-invasive test that allows whole-body imaging and had shown high sensitivity in previous pilot studies.[8,9]

The number of occult malignancies detected with the limited screening strategy was four (2·0%) of 197 patients versus 11 (5·6%) of 197 in the ^{18}F-FDG PET/CT group (absolute risk difference 3·6%, 95% CI −0·4 to 7·9, p=0·065). But, importantly, during a 2-year follow-up of individuals with negative initial screening, a new cancer was diagnosed in only one (0·5%) of 186 patients in the ^{18}F-FDG PET/CT group compared with nine (4·7%) of 193 patients in the limited strategy group (absolute risk difference 4·1%, 95% CI 0·8 to 8·4, p=0·020).

Of note, as also happened in the SOME study, the observed overall rate of occult cancer was notably lower than expected (6% in this case). This might be explained by some characteristics of the study population—eg, 25% of the patients were younger than 50 years, and 6% of the thrombotic events were associated with oral contraceptives. Interestingly, all but one of the malignancies found at initial screening or during