CORRESPONDENCE

Excision Margins in High-Risk Malignant Melanoma

TO THE EDITOR: In their article about excision margins for melanoma, Thomas et al. (Feb. 19 issue)[1] conclude that a 3-cm margin of excision, as compared with a 1-cm margin, is associated with reduced locoregional recurrences. But is a reduction in locoregional recurrence really associated with fewer melanoma-related deaths? Although the incidence of melanoma-related deaths did not differ significantly between the two study groups (P=0.07 in the multivariate analysis), the magnitude of the benefit with respect to melanoma-related survival was similar to the reduction in locoregional recurrence (hazard ratios for death from melanoma and for locoregional recurrence in the group with a 1-cm margin of excision, 1.29 and 1.34, respectively, in the multivariate analysis and 1.24 and 1.26, respectively, in the univariate analysis). The difference in the number of patients with locoregional recurrences in the two groups was 26, and the difference in the number of melanoma-related deaths was 23. How many of those 26 patients with recurrences were in the group of patients who died of melanoma? A significant correlation would strongly support a conclusion regarding causation: persistent locoregional disease is associated with and probably gives rise to metastases and then to death.

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1. Thomas JM, Newton-Bishop J, A'Hern R, et al. Excision margins in high-risk malignant melanoma. N Engl J Med 2004;350:757-66.

TO THE EDITOR: It is critical that Thomas et al. clarify the meaning of "local recurrence," since that phrase has been used to convey two distinctly different meanings: the persistence of a primary melanoma ("true local recurrence")[1] and a metastasis of melanoma ("local recurrence").[2] In the article, however, the authors state, "Local recurrence was defined as a recurrence within 2 cm of the scar or graft." This definition is ambiguous, because such a "recurrence" could be a persistent primary melanoma or a metastasis, and the authors do not offer sufficient evidence for the reader to know the difference.

This ambiguity has profound implications for the meaning of the prognosis for the patients in the study. A group of patients with a "local recurrence" in the sense of persistent primary melanoma would be expected to have a better prognosis than a group of patients with "local recurrence" in the sense of metastasis of melanoma.

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1. Brown CD, Zitelli JA. The prognosis and treatment of true local cutaneous recurrent malignant melanoma. Dermatol Surg 1995; 21:285-90.
2. Karakousis CP, Bartolucci AA, Balch CM. Local recurrence and its management. In: Balch CM, Houghton AN, Sober AJ, Soong S, eds. Cutaneous melanoma. 3rd ed. St. Louis: Quality Medical Publishing, 1998:155-62.

THIS WEEK'S LETTERS

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THE AUTHORS REPLY: We agree with Dr. Hurt that it is important to distinguish between local recurrences that are due to incomplete excision and those that are due to metastasis. However, it is highly unlikely that a melanoma would not be completely excised with a minimum of a 1-cm margin of macroscopically normal tissue, and there was no histopathological evidence of tumor in the margin.

With regard to the analysis suggested by Dr. Hellman, in our trial, events happened over time, so the correct and most informative summary measures to use are hazard ratios, not crude numbers of events. From the absolute number of events, one can calculate the excess number in one of the treatment groups (in this case, 26), but one cannot identify the individual patients who account for the excess and thus whether death rates are higher in that group.

We are grateful to Drs. Krown and Chapman for their comments in the editorial accompanying our article.[1] They agree that accurate nodal staging is the only established benefit of sentinel-lymph-node biopsy, and any evidence of a survival advantage with selective lymphadenectomy must await the results of the Multicenter Selective Lymphadenectomy Trial. They share our concern about the place of adjuvant interferon therapy for patients with pathological stage III melanoma but stress the potential importance of sentinel-lymph-node biopsy as a means of selecting patients for novel adjuvant therapies such as vaccines. We agree, but data from randomized, controlled trials are required to determine whether there is any survival advantage and to assess morbidity before decisions are made about the ultimate role of sentinel-lymph-node biopsy. Unfortunately, few patients undergoing sentinel-lymph-node biopsy have been enrolled in randomized, controlled trials either to validate the procedure or to investigate adjuvant treatments according to sentinel-node status.

Drs. Krown and Chapman also state that "it is not clear that the findings of the current study will change surgical practice." In their editorial, they do not discuss our overview of three excision-margin trials, which suggested a significant increase in the risk of death from melanoma associated with a narrow margin of excision, as compared with a wide margin (hazard ratio, 1.26; 95 percent confidence interval, 1.06 to 1.50; P=0.008). This evidence suggests that wider margins of excision may improve survival in a proportion of patients.

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1. Krown SE, Chapman PB. Defining adequate surgery for primary melanoma. N Engl J Med 2004;350:823-5.

Alendronate versus Calcitriol for Prevention of Bone Loss after Cardiac Transplantation

TO THE EDITOR: Shane et al. (Feb. 19 issue)[1] found minimal differences between the benefits conferred by alendronate and those conferred by calcitriol, and the authors speculated (as did Lindsay, in an accompanying Perspective article[2]) that combination therapy might improve the response. There is good evidence in the literature on postmenopausal osteoporosis of a synergistic effect when calcitriol is used in combination with an antiresorptive agent (a bisphosphonate or estrogen), as shown in studies of calcitriol combined with cyclical etidronate,[3] with alendronate,[4] or with estrogen.[5,6] The two studies of estrogen both showed significant benefits of the combination, as compared with estrogen alone, at the total hip and trochanter (both weight-bearing and chiefly cortical sites), with no adverse effects at the forearm or spine. Advantages over estrogen have also been shown with respect to the bone mineral density of the total body (excluding the head) — another chiefly cortical measurement.[6] Bone loss after organ transplantation is multifactorial and commonly severe, as it was in the study by Shane et al. (untreated loss at the femoral neck, 6.2 percent at one year).[1] Prevention of bone loss by monotherapy is uncommon. There are thus persuasive reasons for further trials of combination therapy after organ transplantation.

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