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EDITORIAL – MELANOMAS

Can We Better Identify Thin Cutaneous Melanomas That are Likely to Metastasize and Cause Death?

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Most patients with thin primary cutaneous melanomas (Breslow thickness $\leq$ 1 mm) have an excellent outcome, and only a minority experience tumor recurrence and death due to melanoma.[1–3] For example, in the American Joint Committee on Cancer database, which contains information on a large number of patients treated at many international centers, the 10-year melanoma-specific survival for patients presenting with T1 melanomas (i.e., $\leq$ 1.0 mm in thickness) was 92 %.[4] In the United States, Europe, and Australia, the majority of patients with newly diagnosed cutaneous melanomas have thin tumors.[5–8] Therefore, even though fewer than 10 % of patients with thin melanomas will eventually progress, this population constitutes a large number of individuals. It is clearly important to identify these higher-risk patients early in the course of their disease if possible, so that management plans appropriate for the biologic aggression of their tumors can be initiated.

How do we accurately identify these high-risk patients with thin melanomas? Previous studies found that increasing Breslow thickness and mitotic rate (MR) were significantly associated with a greater risk of recurrence and death in patients with thin melanomas, but the prognostic importance of other factors such as age, sex, anatomic location, ulceration, and regression has been less consistently demonstrated.[5,6,9,10] Two recent large studies have addressed this question. One was a population-based study and the other a single-center case–control study, and in both, determinants of prognosis in patients with thin melanomas were evaluated.[11,12] The results of the two studies shed new light on this clinically important matter.

The population-based study analyzed 26,736 patients with thin primary melanomas from the State Cancer Registry in Queensland, Australia, and found a 96 % survival rate after 20 years of follow-up. Increasing tumor thickness and level of invasion, increasing patient age, acral lentiginous and nodular histologic subtypes, male sex, and tumor location in the head/neck region were independently associated with melanoma-specific death.[11]

The case–control study, which analyzed patients with thin melanomas treated at Melanoma Institute Australia (MIA, formerly the Sydney Melanoma Unit), was designed to detect differences in clinical and pathologic parameters between two groups of patients with widely disparate outcomes.[12] From the MIA database, which contains details of more than 35,000 patients, 5,628 patients with single thin primary melanomas diagnosed between 1983 and 2003 were identified. Patients who developed distant metastasis ($n = 178$) were compared with 178 sex-matched control patients who experienced no recurrence. After a median follow-up of 111 months, 140 (79 %) of the patients with distant metastases had died of melanoma. Factors that were independently associated with poorer distant metastasis-free and melanoma-specific survival were increasing Breslow thickness (0.51–0.75 mm and >0.75–1.00 mm, compared with $\leq$0.50 mm), increasing

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depth of invasion (Clark level), ulceration of the primary tumor, increasing MR of the primary tumor, and increasing age at diagnosis of the primary melanoma. Nodular melanomas were more frequently associated with distant metastasis than non-nodular types (88 % vs. 47 %, $p = 0.002$), but the association of melanoma subtype (and specifically nodular vs. non-nodular disease) with metastasis was not independent of other factors.

Patient cohorts from specialist melanoma centers (such as MIA) may not be representative of the general population because they may be biased toward higher-risk or more advanced disease groups, which tend to be preferentially referred to major centers.[13] Such bias was minimized in the MIA case–control study because patients were previously untreated and were selected for the study purely on the basis of primary tumor thickness at the time of presentation.[12] The patient cohort in the MIA study did undergo additional selection to satisfy the study design criteria (sex matching and selection of cases and controls in a 1:1 ratio), producing a study population with a much higher proportion (50 %) of higher-risk patients than expected in the general population (<10 %). Nevertheless, comparison of the results of the MIA study and the population-based study reported by Green et al. is informative.[11–13] The independent associations of Breslow thickness/level of invasion and patient age with outcomes in both studies attest to the strong prognostic value of these parameters in patients with thin melanomas. Other prognostic factors identified in the study by Green et al.[11] were anatomic site and histologic subtype. Independent prognostic factors identified in the MIA study but not in that of Green et al. (presumably because they were not recorded in the registry data) were MR and ulceration. In thin melanomas, MR is usually low and ulceration is infrequent, but these parameters are well-established independent prognostic factors for melanomas >1 mm in thickness.[4,14] It is therefore possible that inclusion of these parameters in the multivariate model of Green et al. might have altered the spectrum of parameters that proved to be independently prognostic, particularly if they were found to interact with one or more covariates in the model. An alternative possibility is that, as a result of its large sample size, the study of Green et al. possessed sufficient statistical power to detect covariates with small effect sizes that might not be apparent in smaller data sets.

Though some questions remain, there is now sufficient published evidence to allow stratification of patients with thin melanomas into those who are at low or higher risk of tumor progression and death due to melanoma.[1,5,6,9,11,12,15] This evidence will assist patient counseling and management decisions. Criteria that classify patients as being at a higher risk include one or more of the following: older age (≥45 years), thicker tumors (>0.75 mm), deeper level of invasion in skin (Clark level IV or V), ulcerated tumors, and mitotically active tumors (MR > 1 per mm^2).[5,6,9,12] Low-risk patients with thin melanomas may be managed conservatively, simply with wide local excision of the primary tumor. Some patients classified as being at higher risk may be offered sentinel lymph node biopsy,[16,17] and it would seem appropriate to recommend more intensive follow-up, as for patients with thicker melanomas, for all patients with high-risk thin cutaneous melanomas.[13,18]

REFERENCES

1. Kalady MF, White RR, Johnson JL, et al. Thin melanomas: predictive lethal characteristics from a 30-year clinical experience. *Ann Surg.* 2003;238:528–35.
2. Salman SM, Rogers GS. Prognostic factors in thin cutaneous malignant melanoma. *J Dermatol Surg Oncol.* 1990;16:413–8.
3. Mansson-Brahme E, Carstensen J, Erhardt K, et al. Prognostic factors in thin cutaneous malignant melanoma. *Cancer.* 1994;73:2324–32.
4. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009;27:6199–206.
5. McKinnon JG, Yu XQ, McCarthy WH, Thompson JF. Prognosis for patients with thin cutaneous melanoma: long-term survival data from New South Wales Central Cancer Registry and the Sydney Melanoma Unit. *Cancer.* 2003;98:1223–31.
6. Gimotty PA, Guerry D, Ming ME, et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol.* 2004;22:3668–76.
7. Reintgen C, Shivers S, Reintgen M, et al. The changing face of malignant melanoma. *J Surg Oncol.* 2010;101:443–6.
8. Crocetti E, Caldarella A, Chiarugi A, et al. The thickness of melanomas has decreased in central Italy, but only for thin melanomas, while thick melanomas are as thick as in the past. *Melanoma Res.* 2010;20:422–6.
9. Leiter U, Buettner PG, Eigentler TK, Garbe C. Prognostic factors of thin cutaneous melanoma: an analysis of the central malignant melanoma registry of the German Dermatological Society. *J Clin Oncol.* 2004;22:3660–7.
10. Guitart J, Lowe L, Piepkorn M, et al. Histological characteristics of metastasizing thin melanomas: a case–control study of 43 cases. *Arch Dermatol.* 2002;138:603–8.
11. Green AC, Baade P, Coory M, Aitken JF, Smithers M. Population-based 20-year survival among people diagnosed with thin melanomas in Queensland, Australia. *J Clin Oncol.* 2012;30:1462–7.
12. Murali R, Haydu LE, Long GV, et al. Clinical and pathologic factors associated with distant metastasis and survival in patients with thin primary cutaneous melanoma. *Ann Surg Oncol.* 2012;19:1782–9.
13. Balch CM, Balch GC, Sharma RR. Identifying early melanomas at higher risk for metastases. *J Clin Oncol.* 2012;30:1406–7.
14. Thompson JF, Soong SJ, Balch CM, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol.* 2011;29:2199–205.
15. Gimotty PA, Elder DE, Fraker DL, et al. Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. *J Clin Oncol.* 2007;25:1129–34.

16. Han D, Marzban SS, Yu D, et al. Sentinel node biopsy is indicated for thin melanomas ≥0.76 mm. *Ann Surg Oncol.* 2012;19(Suppl 1):S24.
17. Murali R, Haydu LE, Quinn MJ, et al. Sentinel lymph node biopsy in patients with thin primary cutaneous melanoma. *Ann Surg.* 2012;255:128–33.
18. Turner RM, Bell KJ, Morton RL, et al. Optimizing the frequency of follow-up visits for patients treated for localized primary cutaneous melanoma. *J Clin Oncol.* 2011;29:4641–6.