Long-term Survival of Patients With Invasive Ultra-thin Cutaneous Melanoma
A Single-center Retrospective Analysis

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INTRODUCTION

Cutaneous melanoma (CM) is a severe type of skin malignancy and is responsible for the majority of skin cancer death. The incidence of this tumor is increasing worldwide especially in the fair-skinned populations. Incidence has been steadily increasing since the mid 1960s and is predicted to continue increasing for at least 2 more decades. However, this trend is associated with a reduction in median tumor thickness according to Breslow depth of invasion and patients with thin CM represent ~70% of the new cases. The increased frequency of thin melanoma in recent decades may be explained by an easier access to skin cancer screening clinics, but also by an overdiagnosis of melanoma by pathologists.

According to both the American Joint Committee on Cancer (AJCC) and the guideline on the diagnosis and treatment of CM of the European Dermatology Forum, malignant lesions with a Breslow ≤ 1.0 mm are considered “thin” melanoma. Breslow tumor thickness is one of the most important histological prognostic factors for primary CM. In the absence of other risk factors (such as ulceration and/or mitotic rate >1/mm²) thin CM presents a good survival rate. The 10-year melanoma survival rate for thin CM ranges from 82% to 97%. There are several epidemiological studies concerning the prognosis at both 5- and 10-year of thin CM whereas prognostic studies in patients with Breslow ≤ 0.5 mm (“ultrathin CM”) have rarely been conducted. The aim of this study was to analyze the survival rate of patient with invasive CM with a Breslow ≤ 0.5 mm after 10 years of follow-up in order to more accurately predict the prognosis of patients with very thin CM. The data of our study may provide a more accurate risk stratification of patients with thin melanoma, which could improve both follow-up strategy and clinician-patient communication after the diagnosis of a thin melanoma.

PATIENTS AND METHODS

A retrospective review of 240 patients diagnosed with single invasive very thin CM was carried out. We identified all subjects with a new diagnosis of very thin CM in the period 1989 to 2004 followed-up for at least 10 years at the Melanoma and Soft Tissue Sarcoma Unit of the Veneto Institute of Oncology. Therefore, patients lost to follow-up before their 10-year visit were not included in the study. The population in this area is mainly Caucasian and fair-skinned. The treatment of these patients affected by CM with Breslow ≤ 0.5 mm consisted of diagnostic excision with 1- to 2-mm margins followed by wider excision to achieve histologically confirmed 1-cm margins in healthy tissue. Recurrence, death from melanoma, and disease-free survival rates were all identified. Other prognostic factors, such as mitotic rate, were not investigated because they were not available for all study patients. Data was obtained for diagnosis, staging, and follow-up of the patients; therefore, the need for institutional review board approval was waived by the local ethics committee for this study. No informed consent was obtained from the patients, given the retrospective nature of the study.
RESULTS
The total number of newly diagnosed invasive ultra-thin CM in the period 1989 to 2004 with a follow-up evaluation for at least 10 years was 240 (88 men and 152 women). Median follow-up was 13, 11 years. Table 1 depicts details on Breslow thickness of newly diagnosed invasive ultra-thin CM. Table 2 shows that, after a follow up of at least 10 years, a total of 221 patients were alive and disease free, 2 died of CM, 11 died of other non-neoplastic diseases, 5 died of other neoplastic diseases different from CM, and 1 patient had a local recurrence; therefore the survival rate for CM death at 10-year follow-up was 99.6%. Table 3 shows other clinical-pathological characteristics of the patients investigated whereas Table 4 includes details of the 2 patients deceased for melanoma.

DISCUSSION
The incidence of CM is increasing and the preponderance of CMs diagnosed today are "thin" in terms of Breslow criteria.3,12 About 40 years ago, it was realized that CMs could be divided into categories with better or worse prognosis through the use of prognostic models. The first simple model (Clark levels of invasion and Breslow thickness) is still in use; in the current AJCC classification other 2 tumor-associated factors have been recognized for thin melanomas: mitotic rate and ulceration, nonetheless thickness remains the single most useful variable.7

Very few studies have evaluated the long-term prognosis of patients with invasive CM showing a Breslow ≤ 0.5 mm. Maurichi et al4 have investigated in a multicenter study the overall survival in patients with ultra-thin CM; they showed that the 12-year overall survival of 803 patients with ultra-thin CM was 96.8%. Einwachter et al13 investigated 428 patients with CM ≤ 0.5 mm thick followed-up for a minimum of 5 years. For the whole group, only 3 patients died for melanoma, but all 3 of these deaths occurred in patients who subsequently developed further thicker primary CM.

The purpose of our study was to analyze the prognosis of patients with invasive CM with Breslow ≤ 0.5 mm after at least 10 years of follow-up from the initial diagnosis. Patients were selected on the basis of at least 10 years of follow-up as several recurrences develop > 5 years after diagnosis, and often 8 to 10 years later.4 In general, melanoma recurrence 10 years after the initial diagnosis is very rare; however, late recurrences are observed, and they seem more common in patients with thin primary lesions.4 In our study, only 2 patient deaths in the whole group were attributed to the primary CM. Of the 2 patient deaths attributed to CM, 1 patient died after 16 years of follow-up and the other patient after 2 years from the initial diagnosis. Our study is the first single-center investigation of invasive

| TABLE 1. Distribution of Patients According to Breslow Depth of Invasion |
|-----------------------------------------------|
| <br>**Melanoma Thickness in mm (Breslow Depth)** | **Number of Patients** |
| 0.01–0.09 | 4 |
| 0.091–0.15 | 9 |
| 0.151–0.2 | 15 |
| 0.201–0.25 | 29 |
| 0.251–0.3 | 35 |
| 0.301–0.35 | 34 |
| 0.351–0.4 | 43 |
| 0.401–0.45 | 44 |
| 0.451–0.5 | 27 |
| **Total** | **240** |

| TABLE 2. Distribution of Patients According to Their Current Status |
|-----------------------------------------------|
| **Currents Status** | **Absolute Frequency** | **Relative Frequency** |
| Alive and disease free | 221 | 0.92 |
| Died of melanoma | 2 | 0.008 |
| Died of other non-neoplastic diseases | 11 | 0.045 |
| Died of other neoplastic diseases different from melanoma | 5 | 0.02 |
| Local recurrence | 1 | 0.004 |
| **Total** | **240** | **1** |

| TABLE 3. Additional Patient and Tumor Characteristics |
|-----------------------------------------------|
| **Sex** | **Male** | **88** |
| **Female** | **152** |
| **Ulceration** | | |
| Not determined | 27 |
| Absent | 205 |
| Present | 8 |
| **Clark level** | | |
| Not determined | 4 |
| II | 149 |
| III | 84 |
| IV | 3 |
| **Mitosis** | | |
| Not determined | 44 |
| <1 | 190 |
| ≥1 | 6 |
| **Location** | | |
| Not determined | 4 |
| Head and neck | 10 |
| Trunk | 117 |
| Superior limb | 36 |
| Inferior limb | 73 |

| TABLE 4. Clinical-Pathological Characteristics of the 2 Deceased Patients |
|-----------------------------------------------|
| **Age** | **68** | **73** |
| **Sex** | **Male** | **Male** |
| **Years of follow-up** | **2** | **16** |
| **Mitotic rate** | **Not determined** | **Not determined** |
| **Ulceration** | **Absent** | **Absent** |
| **Breslow thickness** | **0.43** | **0.3** |
| **Location** | **Trunk** | **Trunk** |
| **Clark level** | **III** | **II** |
ultra-thin CM with a follow-up of at least 10 years and provides the longest median follow-up of this group of patients. These data indicate that patients with ultra-thin CMs are at extremely low risk for systemic spread. This may have some practical implications in relation to staging investigations and follow-up of patients. Moreover, the diagnosis of CM creates intense fear in patients which contrasts with the extremely good prognosis of ultra-thin CM. Therefore these data can be utilized by clinicians in order to reassure patients that the disease is highly unlikely to spread and affect their survival. Limitations of the study were the lack of correlation with other risk factor parameters, in particular, ulceration and mitotic rate.

In conclusion our data indicate that death from CM in the group of patients with Breslow \( \leq 0.5 \text{ mm} \) was a very rare event and that diagnosis at this stage dramatically decreases the risk of developing metastatic tumors to a \(<0.5\%\) also after a 10-year period of follow-up.

REFERENCES

1. Chu VH, Tetzlaff MT, Torres-Cabala CA, et al. Impact of the 2009 (7th edition) AJCC melanoma staging system in the classification of thin cutaneous melanomas. *Biomed Res Int.* 2013:898719.
2. Nikolaou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. *Br J Dermatol.* 2014;170:11–19.
3. Ambrosini-Spaltro A, Dal Cappello T, Deluca J, et al. Melanoma incidence and Breslow tumour thickness development in the central Alpine region of South Tyrol from 1998 to 2012: a population-based study. *J Eur Acad Dermatol Venereol.* 2014;29:243–248.
4. Maurichi A, Miceli R, Camerini T, et al. Prediction of survival in patients with thin melanoma: results from a multi-institution study. *J Clin Oncol.* 2014;32:2479–2485.
5. Crocetti E, Caldarella A, Chiariugi 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;20:422–426.
6. Richetta AG, Bottoni U, Paolino G, et al. Thin melanoma and late recurrences: it is never too thin and never too late. *Med Oncol.* 2014;31:909.
7. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009;27:6199–6206.
8. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline—Update 2012. *Eur J Cancers.* 2012;48:2375–2390.
9. Lyth J, Eriksson H, Hansson J, et al. Trends in cutaneous malignant melanoma in Sweden 1997–2011: thinner tumours and improved survival among men. *Br J Dermatol.* 2015;172:700–706.
10. Dickson PV, Gershenwald JE. Staging and prognosis of cutaneous melanoma. *Surg Oncol Clin N Am.* 2011;20:1–17.
11. Gimotty PA, Guerry D. Prognostication in thin cutaneous melanomas. *Arch Pathol Lab Med.* 2010;134:1758–1763.
12. Elder DE. Thin melanoma. *Arch Pathol Lab Med.* 2011;35:342–346.
13. Einwachter-Thompson J, MacKie RM. An evidence base for reconsidering current follow-up guidelines for patients with cutaneous melanoma less than 0.5 mm thick at diagnosis. *Br J Dermatol.* 2008;159:337–341.