Survival in 31,670 patients with thin melanomas: a Swedish population-based study

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Summary

Background The incidence of cutaneous malignant melanoma (CMM) continues to increase in most countries worldwide and the majority are diagnosed with thin tumours (≤1 mm).

Objectives The aim of the present study was to investigate the melanoma-specific survival (MSS) as well as conditional MSS (CMSS) in patients with thin CMM in Sweden.

Patients and methods Clinical and histological parameters were obtained from the Swedish Melanoma Registry for patients diagnosed with thin CMM between 1990 and 2017. Patients were followed until the end of 2017. MSS as well as CMSS for different thickness groups were calculated using the Kaplan–Meier method and Cox regression analyses were used to calculate for survival differences between thickness groups.

Results There were 31,670 patients included for final analyses. The overall 10- and 20-year MSS for thin CMMs was 97% [95% confidence interval (CI) 97–97] and 95% (95% CI 95–96), respectively. From 0.7 mm and above, MSS decreased significantly with increasing thickness level. All thickness groups had an increased survival over time. The lowest CMSS was confirmed for men with 0.1–0.5 mm thickness but their 10-year CMSS increased steadily over time. Women had overall better MSS as well as CMSS than men. However, the relation between MSS and CMSS was similar for both sexes.

Conclusions MSS was confirmed as excellent for patients with thin CMMs in Sweden. Although we could show a decreased MSS for patients with 0.7 mm thickness and above, the long-term survival and, in addition, a very favourable CMSS for those patients do not support more extended follow-up programmes than the current recommendations in Sweden.

What is already known about this topic?
- The majority of patients with cutaneous malignant melanoma are diagnosed with thin melanomas (≤1 mm) and the survival is generally reported as favourable.

What does this study add?
- Our national population-based designed study, including 31,670 patients with thin melanomas, is exclusive when it comes to melanoma survival data, as many former
The incidence of cutaneous malignant melanoma (CMM) continues to increase in most countries worldwide.\textsuperscript{1–3} Breslow thickness of the primary CMM is a crucial predictor for prognosis in localized melanoma.\textsuperscript{4–8} Patients with thin CMMs, tumour thickness according to Breslow of $\leq 1\,\text{mm}$, generally have a favourable prognosis with a very low mortality. The 10-year survival rate is reported between 82% and 98%.\textsuperscript{9–13} However, as the great majority of patients with CMMs are diagnosed with thin tumours, a greater number of deaths occur among patients within this thickness group.

Factors that may predict a worse prognosis in patients with thin CMMs are the presence of ulceration, dermal mitoses, male sex and older age.\textsuperscript{6,9,10,13} A Breslow thickness of 0–8 mm and above has also been confirmed as an unfavourable prognostic parameter and in the most recent edition of the American Joint Committee on Cancer (AJCC) staging manual, this is a cutoff for the subdivision of T1a and T1b CMMs in addition to consideration of ulceration.\textsuperscript{11,14} In the analyses that the AJCC 8th edition is based on, the 5- and 10-year survival rates for T1a tumours were 99% and 98%, respectively, and the corresponding numbers for T1b were 99% and 96%. In 2012, Green et al. showed an overall 20-year melanoma-specific survival (MSS) of 96% in a population-based cohort from Queensland, Australia, of more than 26 000 patients with thin melanomas.\textsuperscript{12}

In a recent study from the Melanoma Institute Australia (MIA), long-term follow-up of 2117 patients with thin CMMs is reported.\textsuperscript{13} The authors presented a marked drop in survival between 0.8 and 0.9 mm and the MSS for patients with tumour thickness 0.9–1.0 mm was significantly reduced compared with patients with tumours of $\leq 0.8\,\text{mm}$ in Breslow thickness. The 10- and 20-year MSS was reported to be 81% and 71%, respectively, for the 0.9–1.0 mm group and 93% and 86%, respectively, for the $\leq 0.8\,\text{mm}$ group. Moreover, they confirmed that the majority of patients who died due to thin CMMs, did so more than 5 years after diagnosis.

In contrast to MSS, which is to be considered a ‘static’ prediction of survival, conditional MSS (CMSS) is a useful concept to provide information on how prognosis develops over time.\textsuperscript{15} The CMSS rate presents the probability of surviving a further $x$ years, given that the patient has already survived $y$ years after the initial diagnosis. There are a number of studies that have confirmed improved survival with time for patients with melanoma.\textsuperscript{16–19} The information of conditional survival is valuable for the patients and clinicians in the follow-up situation as well as in planning for surveillance programmes.

The aim of the present study was to investigate survival, overall MSS as well as CMSS, with special consideration of Breslow thickness, in patients diagnosed with clinically localized thin CMM in Sweden.

**Patients and methods**

In 1990 the national multiprofessional Swedish Melanoma Study Group initiated the Swedish Melanoma Registry (SweMR). Ever since, clinico-pathological data for all CMMs in Sweden has been prospectively collected into the SweMR. This includes important prognostic variables such as sex, age, tumour thickness, tumour localization, ulceration, Clark level of invasion, mitoses (since 2009) and the result from sentinel lymph node biopsy (SLNB, since 2007). By law, clinicians and pathologists are obliged to report all cancer diagnoses to the Swedish National Cancer Registry, thereby ensuring a high quality in the reported data. Every CMM diagnosis is also linked to the patient’s unique individual Swedish personal identity number, which secures linking of records to the national Cause of Death Registry.

Between 1990 and 2017 there were 63 117 cases with primary CMM registered in the SweMR with a coverage rate of 99% compared with the Swedish National Cancer Registry. Out of these 34 129 (54%) were defined as thin (T1) melanomas. According to the AJCC 8th edition melanoma staging manual, stage T1 ($\leq 1\,\text{mm}$) includes tumours up to 1.04 mm and thickness should be expressed with one decimal. T1a and T1b were also defined according to the AJCC 8th edition. More details of current classification of thin melanomas according to AJCC 8th edition is explained elsewhere.\textsuperscript{14} As the aim was to study patients with clinically localized thin melanomas at diagnosis, patients with clinical N or M positivity at diagnosis were excluded. Furthermore, only the first invasive T1 CMM during the study period was included. This resulted in 31 670 patients for further analyses. The Swedish Ethical Review Boards approved the study (Dnr 99160/1999).

**Statistical analysis**

The primary endpoint was MSS and survival time was calculated from the date of diagnosis until the date of the event or to the date of censoring. In the survival analyses, death from CMM was selected as the primary event. Censoring before the final follow-up date of 31 December 2017 was made at the following causes and time points: emigration,
diagnosis of a second CMM and death from causes other than CMM. Patients were divided into five subgroups according to tumour thickness, expressed in mm with one decimal point: ≤ 0.6, 0.7–0.8, 0.9–1.0, 1.0–1.4 and ≥ 1.5 mm. The median tumour thickness was 0.9 mm (IQR 0.8–1.1 mm). The most common location of the primary CMM was the trunk. The presence of ulceration and mitoses were reported in 3.9% and 13.1%, respectively, although the missing proportion on information of mitoses was considerable, 54%, as this parameter was introduced first in the SweMR during 2009. The majority of the patients were diagnosed with T1a melanomas (61%). SLNB was performed in 4.0% of the patients with an overall SLN positivity rate of 0.7% and 50% of those died of melanoma during follow-up.

## Results

A total of 31 670 patients with clinically localized T1 CMMs, diagnosed between 1990 and 2017, were eligible for final inclusion in the study. The median age was 60 years [interquartile range (IQR) 47–71 years] and women were in a slight majority, 53%. The median tumour thickness was 0.6 mm (IQR 0.4–0.8 mm). The most common location of the primary CMM was the trunk. The presence of ulceration and mitoses were reported in 3.9% and 13.1%, respectively, although the missing proportion on information of mitoses was considerable, 54%, as this parameter was introduced first in the SweMR during 2009. The majority of the patients were diagnosed with T1a melanomas (61%). SLNB was performed in 4.0% of the patients with an overall SLN positivity rate of 0.7% and 50% of those died of melanoma during follow-up.

The median follow-up was 6.7 years (IQR 2.8–13.0). The overall 5-, 10-, 15-, 20- and 25-year MSS for thin (T1) CMMs was 98% (95% CI 98–99), 97% (95% CI 97–98), 96% (95% CI 96–98), 95% (95% CI 95–96) and 95% (95% CI 94–95), respectively. The 10-year MSS figures for T1a and T1b were 98% (95% CI 98–99) and 94% (95% CI 94–95), respectively. In total, 727 (2.3%) patients died due to thin CMM during follow-up and 50% of those died within 5 years of diagnosis, while 18.6% were deceased after 10 years of diagnosis. Figure 1 describes the 10-year MSS for individual thicknesses of T1 CMMs. Between 0.6 mm and 0.7 mm there was visually a more pronounced decline with nonoverlapping 95% CIs in MSS, and with further increasing thickness the decline was linear rather than a horizontal shape as with thickness less than 0.6 mm. In Figure 2, long-term survival (5–25 years) is presented graphically for each thickness group. As shown, all lines are separated except for 0.7 and 0.8 mm. In Cox model 1, the HRs increased significantly with increasing thickness level when compared with ≤ 0.6 mm as a reference group: 0.7 mm (HR 2.2; 95% CI 1.7–2.7; P < 0.001), 0.8 mm (HR 2.0; 95% CI 1.6–2.6; P < 0.001), 0.9 mm (HR 3.3; 95% CI 2.6–4.1; P < 0.001) and 1.0 mm (HR 4.9; 95% CI 4.0–6.0; P < 0.001). After adjusting for CMM-related risk factors in Cox model 2, the HRs for thickness were slightly lower: 0.7 mm (HR 2.0; 95% CI 1.5–2.6; P < 0.001), 0.8 mm (HR 1.7; 95% CI 1.3–2.3; P < 0.001), 0.9 mm (HR 1.5; 95% CI 1.2–1.9; P < 0.001), 1.0 mm (HR 1.4; 95% CI 1.1–1.8; P < 0.001), and so on. The Kaplan–Meier method was used to estimate 10-year MSS rates and 95% confidence intervals (CIs) for individual tumour thicknesses of thin melanomas. Ten-year MSS was also calculated 0, 5 and 10 years after diagnosis for each subgroup (≤ 0.6; 0.7–0.8; 0.9–1.0 mm) to investigate whether the risk of dying changed over time. All survival analyses were stratified by sex. Two Cox regression analyses (1, adjusted for age and sex; and 2, further adjusted for tumour localization, ulceration and Clark level of invasion) were used to calculate the differences in MSS survival between the different thickness groups. In the Cox analyses, ≤ 0.6 mm was used as the reference and the results are presented as hazard ratios (HRs) with 95% CIs and P-values. The level of significance was 0.05 and all P-values were two-tailed. All analyses were undertaken using R version 3.3.1 (R Core Team, Vienna, Austria).

### Table 1 Characteristics of 31 670 patients with thin melanoma (T1)

| Characteristic                  | Number (%) |
|---------------------------------|------------|
| **Sex**                         |            |
| Men                             | 14 804 (46.7) |
| Women                           | 16 866 (53.3) |
| **Age (years)**                 |            |
| < 55                            | 12 373 (39.1) |
| 55–69                           | 10 173 (32.1) |
| 70+                             | 9124 (28.8)  |
| **Localization**                |            |
| Extremities                     | 13 284 (41.9) |
| Trunk                           | 14 869 (46.9) |
| Head/neck                       | 3425 (10.8)  |
| Missing                         | 92 (0.3)    |
| **Tumour thickness (mm)**       |            |
| ≤ 0.6                           | 19 140 (60.4) |
| 0.7–0.8                         | 3769 (11.9)  |
| 0.9                             | 3509 (11.1)  |
| 1.0                             | 2780 (8.8)   |
| Missing                         | 2472 (7.8)   |
| **Ulceration**                  |            |
| No                              | 26 608 (84.0) |
| Yes                             | 1245 (3.9)   |
| Missing                         | 3817 (12.1)  |
| **Clark level of invasion**     |            |
| II                              | 15 740 (49.7) |
| III                             | 13 074 (41.3) |
| IV–V                            | 2569 (8.1)   |
| Missing                         | 287 (0.9)    |
| **Mitoses**                     |            |
| < 1 per mm² (absent)            | 10 442 (33.0) |
| ≥ 1 per mm² (present)           | 4135 (13.1)  |
| Missing                         | 17 093 (54.0) |
| **T1 subclassification (AJCC 8th)** |          |
| T1–                             | 2752 (8.7)   |
| T1a                             | 19 554 (61.7) |
| T1b                             | 9364 (29.6)  |
| **SLNB**                        |            |
| Not performed                   | 30 391 (96.0) |
| Performed                       | 1279 (4.0)   |
| **SLN result (N = 1279)**       |            |
| Negative                        | 1176 (91.9)  |
| Positive                        | 80 (6.3)     |
| Missing                         | 23 (1.8)     |

AJCC, American Joint Committee on Cancer; SLN, sentinel lymph node; SLNB, SLN biopsy. AJCC 8th edition staging system: T1–, tumours < 0.8 mm with missing information on ulceration; T1a, < 0.8 mm without ulceration; T1b, < 0.8 mm with ulceration or ≥ 0.8 mm regardless of ulceration.
0.9 mm (HR 2.7; 95% CI 2.0–3.6; \( P < 0.001 \)) and 1.0 mm (HR 3.7; 95% CI 2.8–4.8; \( P < 0.001 \)). Ulceration, higher Clark level of invasion, head/neck localization, older age and male sex were also parameters with significantly negative impact on MSS (Table 2).

The 10-year CMSSs are presented in Table 3. Men and women were also analysed separately. All tumour thickness subgroups had an increased survival over time. The lowest CMSS was confirmed for men with 1.0 mm in thickness but their 10-year CMSS increased steadily over time. For the whole cohort of patients with tumour thickness of 1.0 mm CMSS was 92% (95% CI 90–93) at diagnosis of the primary CMM and further increased after additional 5 and 10 years to 93% (95% CI 92–93) and 96% (95% CI 94–98), respectively. Women had overall better MSS as well as CMSS than men. However, the relation between MSS and CMSS was similar for women and men.

Discussion

To our knowledge this is the largest cohort of patients with thin (T1) CMMs where MSS as well as CMSS are presented. These data could confirm a very favourable survival and in addition deliver an improving CMSS showing that the risk of dying of a thin CMM in Sweden decreases with time passed from the diagnosis of the primary tumour. These results are in line with most other studies investigating MSS as well as CMSS for thin CMMs.\(^1\)^\(^1\),\(^1\),\(^2\)\(^0\) In a large population-based Dutch study they could confirm improved prognosis for melanoma survivors with each additional year of survival after diagnosis except for patients with thin melanoma. For the group of approximately 20 000 patients with thin melanomas the 5-year conditional relative survival actually remained at almost 100% several years after diagnosis in that study.\(^1\)\(^9\)

Sometimes relative survival is used instead of MSS in prognostic studies of thin CMMs. However, we think that MSS is a more appropriate estimate than relative survival in patients with thin CMMs because of the low death rate and the possible confounder of higher socioeconomic status for patients with melanoma compared with the general population resulting in survival estimates above 100%.\(^2\)\(^1\)–\(^2\)\(^3\)

Although vital status and causes of death are reported routinely and annually to the SweMR, we are aware of the possible limitations of using national cause of death registry data as it may affect the outcome of disease-specific survival analyses. Reliability and accuracy of reported causes of death is shown to be different for different diagnoses as well as age groups. Validity has been suggested to be less in the elderly and better among patients deceased from malignant diagnoses.\(^2\)\(^4\) Due to the high numbers of patients in the current study, it would be

![Figure 1](https://example.com/figure1.png)

**Figure 1** Ten-year melanoma-specific survival for different thicknesses in patients with thin melanoma. CI, confidence interval; CMM, cutaneous malignant melanoma.
impossible to review all patient records for cause of death; hence, we had to rely on our cause of death registry data. To use cause of death registry data is also in line with methods used in earlier similar studies.12

The recent decades of rising numbers of thinner CMMs and the risk of overdiagnosis, i.e. the diagnosis of biologically harmless CMMs, must also be considered when discussing survival estimates in thin CMMs. It is known that thinner CMMs are more difficult to diagnose correctly, clinically as well as histopathologically, than thicker melanomas.25 The increased melanoma awareness in the population together with the risk of overdiagnosis of harmless tumours might contribute to very favourable survival estimates.26,27

The findings of better survival in females and decreasing survival with increasing age in the present study are consistent with other studies.12,28 We did not confirm a cutoff at 0·8 mm as in Lo et al.,13 instead, we did see a drop at 0·6 mm and confirmed that in patients with T1 stage disease of up to 0·6 mm there was a negligible risk of dying from CMM. The MSS was still favourable in thin CMMs with a thickness above 0·6 mm in our cohort of patients with thin (T1) CMMs even though the risk of dying from melanoma significantly increased with every 0·1 mm of thickness. Nevertheless, the long-term MSS for the least favourable 1·0-mm subgroup in Sweden was substantially better than the subgroup of 0·9–1·0 mm in the MIA study.15 The significance of tumour thickness as the strongest predictor for survival decreased, but remained in the higher thickness subgroups when ulceration and Clark level of invasion were taken into account. The minimum follow-up time of 10 years in the MIA study is impressive and possibly affects the outcome in survival. However, even though we had a shorter follow-up time we could present quite a fair number of patients at risk 20 years after diagnosis, most probably justifying the reliability of our better long-term results concerning MSS.

It is known that survival estimates based on cohorts of patients treated at specialized referral centres are generally more negative than results given from population-based studies. Hence, the results from the present study are more consistent with the large population-based study from Green et al.,12 which presented a very similar long-term MSS. As shown in the MIA study, patients referred to their clinic but initially treated elsewhere, had poorer prognosis compared with those initially treated at MIA. The frequency of SLNB, as well as the SLN positivity rate, did not differ much between our cohort and the MIA cohort and possibly could not explain the differences in survival outcome between the two studies.

Many melanoma centres usually have very intense follow-up programmes for several years, including monitoring of patients with thin localized CMM. However, according to Swedish National Guidelines, at clinical stage IA (including T1a), the recommended follow-up is generally not more than one postoperative visit including a physical examination with full-body skin examination and clinical lymph node status (if not already performed preoperatively).29 Moreover, information about melanoma, how to self-examine the skin and lymph node regions and also advice concerning sun protection is given. For clinical stage IB, which includes T1b, the

![Figure 2 Long-term melanoma-specific survival for patients with thin melanoma.](image-url)
Table 2  Multivariable Cox proportional hazard regression of melanoma-specific survival related to tumour thickness for thin cutaneous malignant melanoma (CMM) (≤ 1-0 mm)

| Tumour thickness (mm) | Patients, n (CMM deaths) | Model 1* n = 31 670 | Model 2b n = 27 572 |
|-----------------------|--------------------------|---------------------|---------------------|
|                       | Patients, n (CMM deaths) | HR (95% CI) P-value | Patients, n (CMM deaths) | HR (95% CI) P-value |
| ≤ 0.6                 | 19 140 (245)             | 1 (ref)             | 1 671 (183)          | 1 (ref) |
| 0.7                   | 3769 (108)               | 2.2 (1.7–2.7) < 0.001 | 3296 (87)          | 2.0 (1.5–2.6) < 0.001 |
| 0.8                   | 3509 (90)                | 2.0 (1.6–2.6) < 0.001 | 3056 (71)          | 1.7 (1.3–2.3) < 0.001 |
| 0.9                   | 2780 (113)               | 3.3 (2.6–4.1) < 0.001 | 2432 (100)         | 2.7 (2.0–3.6) < 0.001 |
| 1.0                   | 2472 (161)               | 4.9 (4.0–6.0) < 0.001 | 2117 (127)         | 3.7 (2.8–4.8) < 0.001 |

Sex
- Men: 14 804 (396) 0.7 (0.6–0.8) < 0.001
- Women: 16 866 (331)

Age (years)
- < 55: 12 373 (256) 1 (ref)
- 55–69: 10 173 (240) 1.2 (1.0–1.5) < 0.001
- 70+: 9124 (231) 2.0 (1.7–2.4) 0.006

Localization
- Extremities: 11 616 (202) 1 (ref)
- Trunk: 13 047 (285) 1.1 (0.9–1.4) 0.01
- Head/neck: 2909 (81) 1.6 (1.2–2.1) < 0.001

Ulceration
- Absent: 26 345 (483) 1 (ref)
- Present: 1227 (85) 2.3 (1.8–2.9) < 0.001

Clark level of invasion
- II: 13 872 (181) 1 (ref)
- III: 11 376 (290) 1.3 (1.0–1.6) 0.009
- IV–V: 2324 (97) 1.7 (1.2–2.2) < 0.001

CI, confidence interval; HR, hazard ratio. *Model 1 is adjusted for sex and age. **Model 2 is adjusted for sex, age, tumour localization, tumour ulceration and Clark level of invasion. Patients were excluded from model 2 if there were missing data on any of the included variables.

Table 3 Ten-year conditional melanoma-specific survival (CMSS) (%)

| Tumour thickness (mm) | Number of patients after year | 10-year CMSS, % (95% CI) |
|-----------------------|-------------------------------|--------------------------|
|                       | 0 5 10 15 20                  | At 0 years At 5 years At 10 years |
| Total                 |                               | 98 (98–99) 98 (98–99) 99 (98–99) |
| ≤ 0.6                 | 19 140 11 436 6691 3717 1820 | 98 (98–98) 98 (98–99) 99 (98–99) |
| 0.7                   | 3769 2306 1330 765 350        | 96 (95–97) 97 (96–98) 98 (97–99) |
| 0.8                   | 3509 2060 1161 640 296        | 96 (95–97) 96 (95–97) 98 (98–99) |
| 0.9                   | 2780 1732 1037 563 226        | 95 (93–96) 95 (94–97) 96 (95–98) |
| 1.0                   | 2472 1530 841 468 203         | 92 (90–93) 93 (92–95) 96 (94–98) |

Men
- ≤ 0.6: 8836 4983 2768 1466 679 | 98 (98–98) 98 (98–99) 99 (98–99) |
- 0.7: 1758 1035 579 327 144 | 96 (94–97) 97 (95–98) 97 (95–99) |
- 0.8: 1661 938 506 269 97 | 95 (93–96) 95 (93–97) 97 (94–99) |
- 0.9: 1344 789 449 249 89 | 94 (92–96) 95 (93–97) 96 (94–98) |
- 1.0: 1205 725 363 199 88 | 90 (88–93) 92 (89–94) 95 (92–98) |

Women
- ≤ 0.6: 10 304 6453 3923 2251 1123 | 99 (98–99) 99 (98–99) 99 (99–99) |
- 0.7: 2011 1271 751 438 206 | 96 (95–97) 97 (96–98) 99 (97–100) |
- 0.8: 1848 1122 655 371 199 | 97 (96–98) 97 (96–98) 100 (99–100) |
- 0.9: 1436 943 588 314 137 | 95 (94–97) 96 (94–97) 97 (95–99) |
- 1.0: 1267 805 478 269 115 | 93 (91–95) 95 (93–97) 96 (94–99) |

CI, confidence interval; MSS, melanoma-specific survival
recommendation is, in addition to examinations and information given to stage IA patients, an annual clinical examination for 3 years after diagnosis.\textsuperscript{29} Previous studies, based on data from the SweMR, have shown that the majority of recurrences in patients with clinical stage I and II are confirmed within the first years after diagnosis at a median time of 2-3 years. The vast majority of recurrences were diagnosed at body sites easily detected by the patients themselves, which emphasizes the importance of self-examination education.\textsuperscript{30,31}

Our reported long-term survival of thin CMMs is close to that of the general population. It is important to assure and reassure about the excellent outcome for the vast majority of patients with thin CMMs. Most patients diagnosed and treated for thin localized CMMs could possibly safely avoid follow-up programmes other than self-examinations.

An excellent long-term MSS was confirmed for patients diagnosed with clinically localized thin (T1) CMMs in Sweden. Although we could show a decreased MSS for patients with 0-7 mm and above, the long-term survival and in addition a very favourable CMSS for those patients support the rationale of current Swedish national follow-up recommendations. We recommend that our guidelines be followed until future studies have shown proof for even more specific and firm subsets of patients with localized and early-stage melanoma disease that would benefit from more extended follow-up. These high-risk patients will most probably be identified through a combination of already known negative prognostic factors in addition to specific genetic signatures of the primary thin CMM.

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