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Research Paper

# The impact of prognostic factors and comorbidities on survival in older adults with stage I – III cutaneous melanoma in Southwest Finland: A register study

Kalle E. Mattila [a,b,*], Helmi Vihinen [a,c], Eetu Heervä [b], Maria S. Nuotio [d], Pia Vihinen [a]

[a] Department of Oncology, Fican West Cancer Centre, University of Turku and Turku University Hospital, Finland
[b] InFLAMES Research Flagship Center, University of Turku, Finland
[c] Turku School of Economics, University of Turku, Finland
[d] Department of Geriatric Medicine, University of Turku and Turku University Hospital, Finland

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ABSTRACT

*Introduction:* Despite being diagnosed with thicker and more often ulcerated melanomas, cancer-specific survival (CSS) is not necessarily inferior in older adults with melanoma compared to younger patients.

*Materials and Methods:* Our aim was to evaluate the impact of baseline melanoma-specific prognostic factors and comorbidities on recurrence-free survival (RFS), CSS, and overall survival (OS) in patients aged 70–79 ($n = 474$) and ≥ 80 years ($n = 286$) with resected stage I – III cutaneous melanoma in Southwest Finland between January 1, 2000 and December 31, 2020. Patients were restaged according to the 8th edition of TNM classification, and comorbidities were assessed using the Charlson Comorbidity Index (CCI).

*Results:* Patients aged ≥80 years had thicker and more commonly ulcerated melanomas: 43.0%, 40.9%, and 16.1% of patients aged ≥80 and 56.5%, 25.3%, and 18.1% of patients aged 70–79 years were diagnosed with stage I, II, and III melanoma, respectively. Multiple comorbidities (CCI ≥2) were more common and sentinel lymph node biopsy less frequently performed in patients aged ≥80 years. RFS and CSS were similar in patients aged 70–79 years and ≥ 80 years: median RFS 13.8 years vs not reached, with the hazard ratio of melanoma recurrence or death from melanoma 1.25 (95% confidence interval [CI]: 0.91–1.71); median CSS was not reached, with the hazard ratio of death from melanoma 1.12 (95%CI: 0.81–1.75). The proportion of patients who were alive with melanoma recurrence or had died from melanoma was similar in both age groups. In multivariable analysis, higher pathological stage was the only independent risk factor for short RFS regardless of age group, sex, CCI, and tumor ulceration. Higher stage and male sex were associated with short CSS. Age ≥ 80 years, stage III disease, and CCI ≥ 2 were associated with short OS and female sex with long OS in multivariable analysis.

*Discussion:* Pathological stage was the most influential factor determining RFS and CSS in older adults with resected stage I – III melanoma. Concerning OS, age ≥ 80 years, stage III disease, and multiple comorbidities had a significant negative impact.

## 1. Introduction

Over the last decades, the incidence of cutaneous melanoma has increased globally in countries with fair-skinned populations mostly due to increased exposure to ultraviolet radiation [1,2]. According to a Danish study, the incidence of melanoma has increased in the Nordic countries from 1980s to 2010s in all age-groups, but especially in adults aged ≥70 years [3]. A similar pattern was seen in the Netherlands from 1989 to 2015 [4]. Consistently, there was a five-fold higher incidence of cutaneous melanoma among older males (135.3 and 61.7 /100,000 person-years for males and females aged ≥70 years, respectively) compared to males and females aged 20–69 years (25.7 and 27.6 /100,000 person-years, respectively) in Finland in 2021 [5,6]. Together with the increasing incidence of cutaneous melanoma, the number of

* Corresponding author at: Department of Oncology, Turku University Hospital, FICAN West Cancer Centre, InFLAMES Research Flagship Center, POB 52, FIN-20521 Turku, Finland.
*E-mail address:* kalle.mattila@tyks.fi (K.E. Mattila).

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older adults is growing globally [7]. Thus, it has become more common for physicians to encounter older adults with cutaneous melanoma.

Cutaneous melanomas diagnosed at an early stage are likely cured with a surgical resection involving sentinel lymph node biopsy (SLNB). The five-year overall survival (OS) rates of patients with early stage, localized melanoma (stage I and II) have ranged from 97 to 99% to 82–94%, respectively, whereas five-year OS rates are significantly lower (32%–93%) in patients with satellite, in-transit, or local lymph node metastases (stage III melanoma) [8]. Currently, completion lymph node dissection (CLND) after positive SLNB is less frequently performed since it did not improve cancer-specific survival (CSS) compared to observation, but SLNB is well-established as a prognostic procedure revealing patients in need of adjuvant treatment [1]. Adjuvant treatment with immune checkpoint inhibitors and targeted therapies has prolonged recurrence-free survival (RFS) in patients with stage III melanoma and, recently, also in high-risk stage II melanoma [1,9]. In older adults, however, comorbidities and impaired functional ability might lead to delays in the diagnosis of primary melanoma and a tendency towards more conservative treatment that could affect their prognosis [10].

Older age has been associated with thicker and ulcerated melanomas [4,11–16], less frequent SLNBs [13,14,17], and suboptimal surgical margins resulting in a higher risk for local disease recurrence [13–15]. In the Surveillance, Epidemiology, and End Results (SEER) data, it was observed that age $\geq$ 80 years was associated with lower rate of CLND, targeted therapies, and immunotherapy in patients with stage III melanoma [16]. Toxicity from systemic treatment might be intolerable in older adults in the adjuvant and metastatic setting, although targeted therapies and PD-1 inhibitors have been feasible in older adults with metastatic melanoma [18–21]. However, treatment discontinuation due to adverse events was more common with increasing age [21]. Although it has been highlighted that older adults with melanoma should be treated according to prognostic factors rather than advanced age [22], comorbidities and performance status must be carefully considered when deciding the optimal treatment.

Despite unfavorable prognostic factors and suboptimal surgical treatment, shorter CSS has not been observed in patients aged $\geq$85 years compared to patients aged 65–84 years with early-stage melanoma [15]. In this retrospective, register-based study, our aim was to evaluate the impact of baseline melanoma-specific prognostic factors and comorbidities on the RFS, CSS, and OS of patients in age groups 70–79 years and $\geq$ 80 years with resected localized cutaneous melanoma and lymph node metastases in Southwest Finland.

## 2. Materials and Methods

### 2.1. Study Population

In Southwest Finland, the treatment of cutaneous melanoma is centralized into Turku University Hospital. In this retrospective cohort study, we used a previously published melanoma cohort covering the years 2005–2019 [23], extended to cover the years 2000–2020. We initially identified 884 patients aged $\geq$70 years at the diagnosis of cutaneous melanoma from the electronic medical records of the hospital district of Southwest Finland. Patients with missing pathological stage ($n$ = 16), in-situ melanoma (stage 0, $n$ = 49), and synchronously metastatic melanoma (stage IV, $n$ = 59) were excluded. The final cohort included 760 patients who had undergone resection of the primary tumor and SLNB, if indicated according to the European treatment guidelines [24], for the treatment of stage I-III cutaneous melanoma. Patients were stratified into two age groups (70–79 years [$n$ = 474] and $\geq$ 80 years [$n$ = 286]) before statistical analyses.

Baseline clinical characteristics at the time of first cutaneous melanoma diagnosis including age, sex, the location of primary melanoma, tumor thickness (Breslow), and ulceration were automatically obtained from electronic medical records. Non-melanoma skin cancer diagnoses and new primary cutaneous melanoma diagnoses during follow-up period were also collected. However, non-melanoma skin cancers, e.g., basal cell carcinomas, are treated mainly in the primary health care units and diagnoses are likely underestimated in this study population.

Data was manually reviewed, and patients were restaged by the study investigators (HV, KEM, EH, PV). The pathological T-stage (pT) and pathological stage (stage I = pT1a, pT1b, pT2a without lymph node, satellite, or in-transit metastases; stage II = pT2b, pT3a, pT3b, pT4a, pT4b without lymph node, satellite, or in-transit metastases; stage III: $T_{any}$ with lymph node, satellite or in-transit metastases) were determined according to the 8th edition of TNM classification of malignant tumors [25] from the first cutaneous melanoma diagnosed during study period. If ulceration was not mentioned in the pathology report (ulceration unknown), patients were considered not to have ulceration and their pathological stage was determined accordingly. The Charlson Comorbidity Index (CCI, where 0 denotes no comorbidities) at the diagnosis of primary melanoma was determined for each patient based on the International Classification of Diseases 10th Revision (ICD-10) diagnoses of comorbidities as described [26]. The parameters evaluated in the CCI included myocardial infarction (1 point), congestive heart failure (1 point), peripheral vascular disease (1 point), cerebrovascular disease (1 point), dementia (1 point), chronic pulmonary disease (1 point), rheumatologic disease (1 point), peptic ulcer disease (1 point), mild liver disease (1 point), diabetes without chronic complications (1 point), diabetes with chronic complications (2 points), hemiplegia or paraplegia (2 points), renal disease (2 points), any malignancy, including leukemia and lymphoma (2 points), moderate or severe liver disease (3 points), metastatic solid tumor (6 points), and AIDS/HIV (6 points).

Information on medical treatments and radiotherapy for melanoma during the study follow-up period was obtained. In the 2000s and 2010s, interferon alpha was used as an adjuvant treatment for young and fit patients with high-risk stage III melanoma until PD-1 inhibitors became available in the adjuvant treatment in Finland in 2018 and dabrafenib plus trametinib in 2020. In routine clinical practice, BRAF targeted therapies have been used for metastatic melanoma in Finland since 2014 and PD-1 inhibitors since 2015. Follow-up information on treatment outcomes included the date of local recurrence, distant metastasis, death from melanoma or other causes, and the last follow-up visit. The study follow-up period ended on July 5, 2022.

### 2.2. Statistical Analyses

Continuous variables are presented with median and range and categorical variables with number and percentages. Differences in the baseline characteristics between age groups were assessed using Chi-squared test for categorical variables and Kruskal-Wallis test for continuous variables.

The index date of survival analyses was the date of the first occurrence of cutaneous melanoma diagnosis (ICD-10 code C43) in electronic medical records. The median length of the follow-up was estimated using a reverse Kaplan-Meier method. The estimated median RFS, CSS, and OS were calculated using Kaplan-Meier log-rank method and provided with 95% confidence intervals (95% CI). Differences in RFS, CSS, and OS between the age groups were described with univariate hazard ratios (HR) and 95% CIs calculated with Cox regression model. RFS was defined as time from the index date to local recurrence (event), metastasis (event), or death from melanoma (event), and patients who were alive without melanoma recurrence or who had died from non-melanoma causes were censored at the date of the last follow-up visit or death. CSS was defined as time from the index date to death from melanoma (event), and patients who were alive or who had died from non-melanoma causes were censored at the date of the last follow-up visit or death. OS was defined as time from the index date to death from any cause (event), and patients who were alive were censored at the date of the last follow-up visit. Recurrence-free survival status (alive without melanoma recurrence; alive with melanoma recurrence; no

melanoma recurrence, non-melanoma cause of death; melanoma recurrence, non-melanoma cause of death; cause of death melanoma) was determined at two years and at five years from the diagnosis of primary melanoma.

Multivariable analyses were performed to study the effect of prognostic factors on survival outcomes (RFS, CSS, and OS). The covariates in the Cox regression model included age (70–79 years, ≥80 years), sex (male, female), CCI (CCI 0—1, CCI ≥2), ulceration (present, no), and pathological stage (I, II, III). The HRs of melanoma recurrence or death from melanoma, death from melanoma, and death from any cause were provided with 95% CI. All analyses were performed using IBM SPSS version 28.0.1.0.

### 2.3. Ethical Approval

The study was approved by the Institutional Review Board of Turku University Hospital (license number T206/2015 and T132/2019). Informed consent was waived due to the retrospective and register-based design of the study. Data was collected and handled according to the legislation on the secondary use of healthcare data in Finland.

## 3. Results

### 3.1. Clinical Characteristics

There were 474 patients aged 70–79 years and 286 patients aged ≥80 years diagnosed with stage I – III cutaneous melanoma at the hospital district of Southwest Finland between January 1, 2000 and December 31, 2020. Baseline clinical characteristics are described in Table 1: patients aged ≥80 years presented more commonly with multiple comorbidities (CCI ≥2), head & neck and acral melanomas, as well as with thicker and ulcerated melanomas leading to increased pathological T-stage and a higher rate of pathological stage II disease compared to patients aged 70–79 years. Despite being diagnosed with thicker melanomas, SLNB was less frequently performed in patients aged ≥80 years. The proportion of patients with satellite, in-transit, or lymph node metastases (stage III) was similar in both age groups.

During follow-up, only five patients (1.7%) aged ≥80 years had received any medical treatment for melanoma as compared to 47 patients (9.9%) among those aged 70–79 years ($p < 0.001$). There were no differences in the use of radiotherapy (39 patients [8.2%] aged 70–79 years vs 15 patients [5.2%] aged ≥80 years, $p = 0.121$). There were no differences in the incidence of new primary melanomas (diagnosed in 34 patients [7.2%] aged 70–79 years vs 13 patients [4.5%] aged ≥80 years, $p = 0.145$) and non-melanoma skin cancers (diagnosed in 61 patients [12.9%] aged 70–79 years vs 41 patients (14.3%) aged ≥80 years, $p = 0.566$).

**Table 1**
Baseline clinical characteristic of patients aged 70–79 years and ≥ 80 years with stage I – III melanoma.

| | Age 70–79 years | Age ≥ 80 years | *p*-value |
|---|---|---|---|
| | *n* = 474 | *n* = 286 | |
| Male | 282 (59.5%) | 151 (52.8%) | 0.071 |
| Female | 192 (40.5%) | 135 (47.2%) | |
| CCI 0–1 | 362 (76.4%) | 179 (62.6%) | <0.001 |
| CCI ≥2 | 112 (23.6%) | 107 (37.4%) | |
| Location head & neck | 117 (24.7%) | 78 (27.3%) | 0.042 |
| Location trunk | 213 (44.9%) | 115 (40.2%) | |
| Location limbs | 140 (29.5%) | 83 (29.0%) | |
| Acral | 4 (0.8%) | 10 (3.5%) | |
| Median tumor thickness mm (range) | 1.3 (0.1—30.0) | 2.1 (0.1—30.0) | <0.001 |
| pT1 | 197 (41.6%) | 83 (29.0%) | <0.001 |
| pT2 | 107 (22.6%) | 60 (21.0%) | |
| pT3 | 84 (17.7%) | 59 (20.6%) | |
| pT4 | 86 (18.1%) | 84 (29.4%) | |
| Ulceration | 102 (21.5%) | 92 (32.2%) | 0.004 |
| No ulceration | 267 (56.3%) | 135 (47.2%) | |
| Ulceration unknown | 105 (22.2%) | 59 (20.6%) | |
| Pathological stage I | 268 (56.5%) | 123 (43.0%) | <0.001 |
| Pathological stage II | 120 (25.3%) | 117 (40.9%) | |
| Pathological stage III | 86 (18.1%) | 46 (16.1%) | |
| SLNB performed in patients with Breslow >1.0 mm (*n* = 480) | 248 (89.5%) | 148 (72.9%) | <0.001 |

CCI=Charlson comorbidity index, pT = pathological assessment of the primary tumor, SLNB = sentinel lymph node biopsy.

### 3.2. Survival Outcomes

After the median follow-up of 63.8 (95%CI: 56.8–70.9) months, 173 melanoma recurrences, 120 deaths from melanoma, and 339 non-melanoma deaths had occurred. There were no differences in RFS or CSS in patients aged 70–79 years compared to patients aged ≥80 years: the median RFS 165 months (13.8 years) vs not reached (NR), the HR of melanoma recurrence or death from melanoma 1.25 (95%CI: 0.91–1.71) (Fig. 1A). The median CSS was not reached in both age groups, the HR of death from melanoma 1.12 (95%CI: 0.81–1.75) (Fig. 1B). OS was longer in patients aged 70–79 years compared to patients aged ≥80 years: the median OS 83.7 (95%CI: 71.8–95.6) months vs 47.8 (95%CI: 39.3–56.4) months, respectively, and the HR of any-cause death 0.44 (95%CI: 0.36–0.54) (Fig. 1C).

When the whole study population was stratified according to pathological stage, the mRFS was NR, 113.4 (95%CI: 48.5–178.3) months, and 31.6 (95%CI: 16.7–46.4) months in patients with stage I, II, and III melanoma, respectively (data not shown). The mCSS was NR, 181.6 (95%CI: N/A) months, and 73.0 (95%CI: 47.2–98.8) months and the mOS was 75.5 (95%CI: 67.7–83.2) months, 54.0 (95%CI: 44.8–63.2) months, and 37.0 (95%CI: 26.9–47.1) months in patients with stage I, II, and III melanoma, respectively (data not shown).

### 3.3. Survival Outcomes According to Stage, Age, and Comorbidities

After stratifying patients according to pathological stage (I, II, or III) and age (70–79 years, ≥80 years) or the CCI (CCI 0–1, CCI ≥2), we observed that there were no differences in the pairwise comparisons of RFS and CSS of patients within the same pathological stage.

RFS and CSS were determined by pathological stage rather than age group (Fig. 2A and B) or comorbidities (Fig. 2D and E): in patients aged 70–79 years and ≥ 80 years with stage I melanoma, the mRFS and the mCSS were not reached. In patients aged 70–79 years with stage II melanoma, the mRFS was 105.5 (95%CI: 73.0–138.0) months and the mCSS was 181.6 (95%CI: 98.5–264.7) months. In patients aged ≥80 years with stage II melanoma, the mRFS and the mCSS were not reached. In patients aged 70–79 years with stage III melanoma, the mRFS was 31.0 (95%CI: 16.8–45.2) months and the mCSS 73.0 (95%CI: 35.4–110.6) months. In patients aged ≥80 years with stage III melanoma, the mRFS was 33.1 (95%CI: 0.2–65.9) months and the mCSS 67.0 (95%CI: 12.4–121.6) months.

In contrast to RFS and CSS, OS was affected by the age group (Fig. 2C) and the CCI (Fig. 2F) in addition to pathological stage: patients aged 70–79 years with stage I and II melanoma had the longest median OS: 93.6 (95%CI: 80.1–106.3) months and 104.3 (95%CI: 68.6–139.9) months, respectively. The mOS of patients aged ≥80 years with stage I melanoma was 58.7 (95%CI: 53.0–64.3) months. The mOS of patients aged ≥80 years with stage II melanoma was shorter (39.2 [95%CI: 30.2–48.4] months) than the mOS of patients aged 70–79 years with stage III melanoma (44.2 [95%CI: 23.9–64.4] months). The mOS of patients aged ≥80 years with stage III melanoma was only 24.1 (95%CI: 18.5–29.6) months.

Patients with stage I melanoma and CCI 0–1 had the longest mOS (81.5 months [95%CI: 69.9–93.0]). Patients with stage I melanoma and CCI ≥2 had a shorter mOS (65.7 [95%CI: 48.9–82.6] months) than patients with stage II melanoma and CCI 0–1 (70.4 [95%CI: 49.9–91.0]

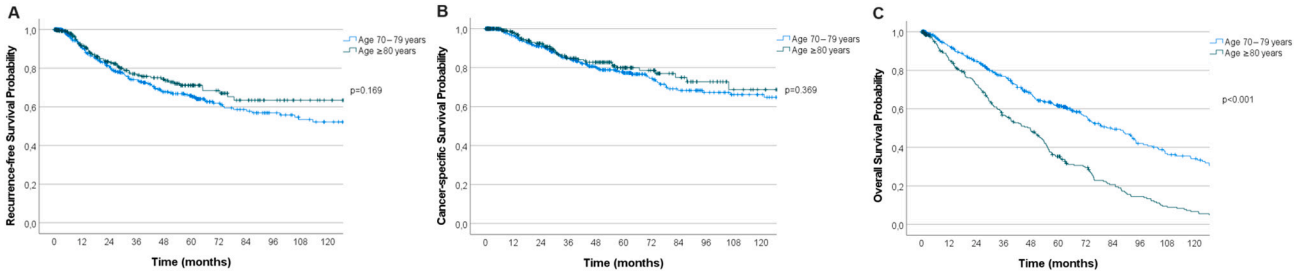


**Fig. 1.** Recurrence-free (panel A), cancer-specific (panel B), and overall survival (panel C) in patients with resected stage I-III melanoma according to age group.

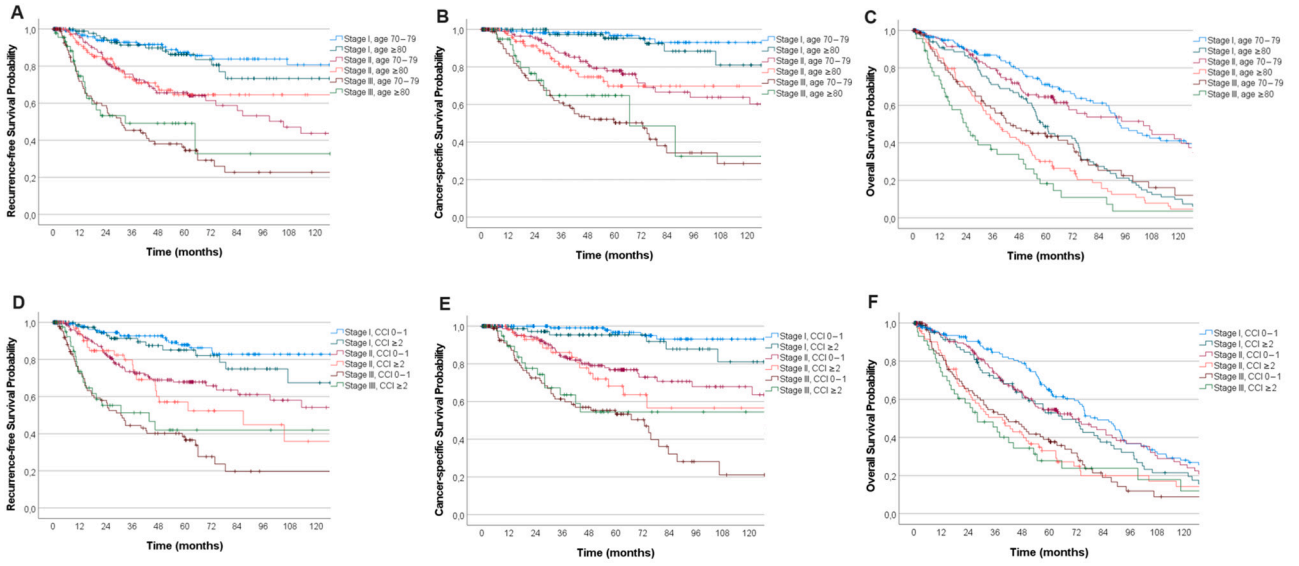


**Fig. 2.** Recurrence-free survival (panel A), cancer-specific survival (panel B), and overall survival (panel C) according to pathological stage and age group and recurrence-free survival (panel D), cancer-specific survival (panel E), and overall survival (panel F) according to pathological stage and the Charlson Comorbidity Index (CCI).

months). Patients with stage II melanoma and CCI ≥2 had the mOS close to patients with stage III melanoma and CCI 0–1 (39.2 [95%CI: 24.4–54.2] months and 41.1 [95%CI: 25.1–57.1] months, respectively).

### 3.4. Two-Year and Five-Year Recurrence-Free Survival Status

There were no differences between patients aged 70–79 years and ≥ 80 years in the number of patients who were alive with melanoma recurrence (2% vs 1% at two years and 4% vs 2% at five years from the primary melanoma, respectively) or died from melanoma (9% vs 8% at two years and 14% vs 12% at five years from the primary melanoma, respectively) (Supplementary Fig. 1). There were statistically significant differences in the two-year ($p < 0.001$) and the five-year ($p < 0.001$) RFS status between age groups due to the larger proportion of patients who had not experienced melanoma recurrence and died from non-melanoma causes in patients aged ≥80 years (5% vs 18% at two years from the primary melanoma and 11% vs 40% at five years from the primary melanoma in patients aged 70–79 years compared to patients aged ≥80 years) (Supplementary Fig. 1).

### 3.5. Multivariable Analyses of Survival Outcomes

In multivariable analysis, higher pathological stage was the only independent risk factor for short RFS regardless of age, sex, CCI, and tumor ulceration (Table 2). The HR of disease recurrence or death from melanoma was 2.56 (95%CI: 1.44–4.56) for patients with stage II melanoma and 6.58 (95%CI: 3.73–11.61) for patients with stage III melanoma compared to patients with stage I melanoma.

Male sex and higher pathological stage were associated with short CSS regardless of age, CCI, and tumor ulceration in multivariable analysis (Table 2). The HR of death from melanoma was 0.60 (95%CI: 0.39–0.93) for female patients compared to male patients. The HR of death from melanoma was 5.91 (95%CI: 2.45–14.28) for patients with stage II melanoma and 13.86 (95%CI: 5.76–33.34) for patients with stage III melanoma compared to patients with stage I melanoma.

Age ≥ 80 years, CCI ≥2, stage III melanoma, and male sex were associated with short OS in multivariable analysis (Table 2). The HR of death from any cause was 2.67 (95%CI: 2.10–3.41) for patients aged ≥80 years compared to patients aged 70–79 years, 1.62 (95%CI: 1.27–2.05) for patients with CCI ≥2 compared to patients with CCI 0–1, and 1.80 (95%CI: 1.30–2.48) for patients with stage III melanoma compared to patients with stage I melanoma. There was no difference in the HR of death from any cause between patients with stage II and I melanoma (HR 1.01 [95%CI: 0.75–1.36]). The HR of any-cause death was 0.66 (95%CI: 0.52–0.83) for female patients compared to male patients.

## 4. Discussion

In this retrospective, register-based study of 760 Finnish patients aged ≥70 years with resected stage I – III cutaneous melanoma, we observed that patients aged ≥80 years more commonly had thicker and ulcerated primary melanomas than patients aged 70–79 years, leading to a higher rate of stage II melanomas, which is in line with previous

**Table 2**
Multivariable analyses of recurrence-free, cancer-specific, and overall survival in patients aged ≥70 years with resected stage I – III melanoma.

| Recurrence-free survival | | |
|---|---|---|
| Covariate | Hazard ratio | p-value |
| Age group ≥80 years (ref. 70–79 years) | 0.98 (95%CI: 0.68–1.40) | 0.896 |
| Female (ref. male) | 0.92 (95%CI: 0.65–1.31) | 0.640 |
| CCI ≥2 (ref. CCI 0–1) | 0.94 (95%CI: 0.64–1.37) | 0.736 |
| Ulceration (ref. no ulceration) | 1.38 (95%CI: 0.96–1.98) | 0.085 |
| Stage II (ref. stage I) | 2.56 (95%CI: 1.44–4.56) | 0.001 |
| Stage III (ref. stage I) | 6.58 (95%CI: 3.73–11.61) | <0.001 |
| **Cancer-specific survival** | | |
| Covariate | Hazard ratio | p-value |
| Age group ≥80 years (ref. 70–79 years) | 1.17 (95%CI: 0.76–1.82) | 0.475 |
| Female (ref. male) | 0.60 (95%CI: 0.39–0.93) | 0.021 |
| CCI ≥2 (ref. CCI 0–1) | 0.94 (95%CI: 0.59–1.49) | 0.788 |
| Ulceration (ref. no ulceration) | 1.16 (95%CI: 0.76–1.78) | 0.489 |
| Stage II (ref. stage I) | 5.91 (95%CI: 2.45–14.28) | <0.001 |
| Stage III (ref. stage I) | 13.86 (95%CI: 5.76–33.34) | <0.001 |
| **Overall survival** | | |
| Covariate | Hazard ratio | p-value |
| Age group ≥80 years (ref. 70–79 years) | 2.67 (95%CI: 2.10–3.41) | <0.001 |
| Female (ref. male) | 0.66 (95%CI: 0.52–0.83) | <0.001 |
| CCI ≥2 (ref. CCI 0–1) | 1.62(95%CI: 1.27–2.05) | <0.001 |
| Ulceration (ref. no ulceration) | 1.27 (95%CI: 0.97–1.64) | 0.078 |
| Stage II (ref. stage I) | 1.01 (95%CI: 0.75–1.36) | 0.946 |
| Stage III (ref stage I) | 1.80 (95%CI: 1.30–2.48) | <0.001 |

ref. = reference, CCI=Charlson comorbidity index, CI=Confidence Interval.

studies showing the association of higher tumor thickness and ulceration with increasing age [4,11–16]. As expected, multiple comorbidities were more common in patients aged ≥80 years compared to patients aged 70–79 years. We found that in Southwest Finland SLNB was less frequently performed in patients aged ≥80 years, as has also observed in France, Australia, and the US, although the rate of SLNB in older adults was considerably high in our study population (73–90%) compared to earlier studies (23–62%) [13,14,17]. Despite higher pathological stage, lower rate of SLNB, and hardly any use of systemic treatments for melanoma, the RFS and CSS of patients aged ≥80 years were not inferior compared to patients aged 70–79 years in this study. Shorter OS was seen in the cohort of patients aged ≥80 years where patients died more often from non-melanoma causes. In multivariable analysis, older age was independently associated with shorter OS, but not with RFS or CSS, resembling the results of Australian patients with early-stage melanoma [14,15].

In earlier studies, younger age (<65–70 years) has been associated with a lower risk of death from melanoma [11,12,14,23] but this has not been seen among patients aged ≥65 years with localized melanoma [14,15]. Despite higher proportion of stage II melanomas in patients aged ≥80 years, CSS was similar in patients aged 70–79 years and ≥ 80 years in our study population. In multivariable analysis, ≥80 years of age was not associated with shorter CSS after adjusted for other prognostic factors in this study adding evidence that advanced age is not associated with a higher risk of death from melanoma in older adults with localized disease. However, as patients with stage II and III melanomas had a significantly higher risk of disease recurrence and death from melanoma compared to patients with stage I melanoma, and stage III disease was associated with an increased risk of any-cause death, there is a constant need to raise awareness of early detection of cutaneous melanomas also among older adults. There are likely several barriers hampering early diagnosis of cutaneous melanomas in patients ≥80 years, including higher incidence of cutaneous malignancies and multiple benign skin lesions as well as impaired vision and functional ability and social factors (e.g., living alone).

In our study population, females had a lower risk of death from melanoma, as well as death from any cause, compared to males as observed earlier in other studies on patients with melanoma [11,12,14,23,27–29]. Survival differences between females and males are suggested to be partly mediated by sex hormones, e.g., estrogen receptor signaling in melanocytes [27,30]. Interestingly, there was no difference in the CSS of females and males aged over 65 years in a German study [11]. In this study, however, the association of female sex with longer CSS and OS was retained when adjusted for age and other relevant prognostic factors in multivariable analysis.

Generally, the prognosis of older adults with resected stage I – II melanoma in our region was good: the mOS of patients aged 70–79 years with stage I and II melanoma was around eight years (7.8–8.7 years) which is similar as that seen in Australian patients aged 65–74 years with stage I and II melanoma (mOS 8.0 years) [14]. Even patients aged ≥80 years with stage I and II melanoma had a mOS of 4.9 and 3.3 years, respectively, in our region. In multivariable analysis, higher age and multiple comorbidities were significantly associated with shorter OS in addition to local lymph node metastases. In a Danish population-based study, it was found that comorbidities deteriorated survival in patients with advanced melanoma [31]. In this study, however, multiple comorbidities had a significant impact on OS regardless of pathological stage in patients with resected localized melanoma. The implementation of comprehensive geriatric assessment (CGA) on the treatment of older adults with multiple cancer types has been shown to reduce toxicity from cancer treatment and improve treatment completion and the quality of life according to systematic reviews [32,33]. Thus, older adults with both early and late-stage melanoma could benefit from geriatric assessments and careful management of comorbid conditions in addition to the treatment and follow-up for melanoma.

The limitations of this study are attributed to its retrospective design. Clinical characteristics were obtained from electronic medical records, but some relevant prognostic characteristics could not be retrieved despite the manual review of medical records. The Eastern Cooperative Oncology Group performance status was missing from 51.1% of patients and body mass index from 23.9% of patients and were therefore omitted from further analyses. As the cause of death was defined only "melanoma" or "non-melanoma" in our database, we were not able to specify non-melanoma-related causes of death in detail. Moreover, systematic CGA was not offered for patient with cancer at Southwest Finland during the study period, which could have contributed to the small number of systemic treatments in older adults. Single-site, retrospective register studies are always vulnerable to selection bias, and there might be differences in real-world results based on differences in patient populations and treatment practices in different sites and countries. However, our results are in line with earlier studies from Europe, Australia, and the US [11,13–16] as well as covering all cases of melanoma as compared to population-based statistics from Finnish Cancer Registry, [34] supporting the generalizability of our findings in the treatment of older adults with melanoma.

## 5. Conclusion

Age and comorbidities were not associated with a higher risk of melanoma recurrence or death from melanoma in patients aged ≥70 years with resected localized melanoma. However, besides pathological stage III melanoma, advanced age and multiple comorbidities had a significant negative impact on OS, underscoring the need of geriatric intervention in addition to the treatment and follow-up for melanoma. Multidisciplinary collaboration involving plastic surgeon, oncologist, dermatologist, and geriatrician is essential to improve treatment outcomes and the quality of life in older adults with melanoma.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101701.

## Disclosures

Kalle E Mattila has received consulting or advisory honoraria from

Astellas, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Ipsen, Janssen, Merck Sharp & Dohme, Merck−Pfizer alliance, Novartis, Roche, and Sanofi.

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Helmi Vihinen, Eetu Heervä, and Maria S Nuotio have nothing to disclose.

## Author Contributions

Conceptualization: Kalle E. Mattila, Maria S. Nuotio, Pia Vihinen. Data curation: Kalle E. Mattila, Helmi Vihinen, Eetu Heervä, Pia Vihinen. Formal analysis: Kalle E. Mattila, Helmi Vihinen, Eetu Heervä, Pia Vihinen. Investigation: Kalle E. Mattila, Helmi Vihinen, Eetu Heervä, Maria S. Nuotio, Pia Vihinen. Methodology: Kalle E. Mattila, Helmi Vihinen, Eetu Heervä, Maria S. Nuotio, Pia Vihinen. Software: Kalle E. Mattila. Supervision: Pia Vihinen. Visualization: Kalle E. Mattila. Writing - original draft: Kalle E. Mattila. Writing - review & editing: Helmi Vihinen, Eetu Heervä, Maria S. Nuotio, Pia Vihinen.

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