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The impact of the coronavirus disease 2019 pandemic on the diagnosis of cutaneous melanomas; a retrospective cohort study from five European skin cancer reference centers

MASTERARBEIT

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vorgelegt von
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1. Zusammenfassung

Einleitung

Die staatlich verordneten COVID-19-Lockdowns hatten einen dramatischen Einfluss auf den Zugang zur medizinischen Grundversorgung. Einige retrospektive Studien zeigen einen Rückgang der Anzahl von Melanomdiagnosen sowie eine Zunahme der Tumordicke nach den COVID-19-Lockdowns. Die daraus resultierende diagnostische Verzögerung lässt erstens ein substanzielles Risiko bezüglich erhöhter Mortalität und Morbidität und zweitens steigende Gesundheitskosten infolge fortgeschrittener Melanome befürchten. Das Ziel dieser Studie war die qualitative und quantitative Untersuchung des Einflusses der COVID-19-Restriktionen auf die Melanomdiagnosen. Insbesondere wurde versucht die Frage zu beantworten, ob es bei der Melanomdiagnose aufgrund der Lockdowns zu Verzögerungen gekommen ist.

Methoden

Die vorliegende retrospektive Studie untersuchte den Einfluss der COVID-19-Lockdowns auf die Melanomdiagnosen in fünf dermatologischen Referenzzentren in der Schweiz, Italien, Deutschland, Österreich und Italien. Insgesamt wurden 7865 histologisch bestätigte Primärmelanome während des Zeitraumes vom 01. September 2018 bis zum 31. August 2021 analysiert. Die Zeitperiode wurde in «pre-lockdown», «lockdown» und «post-lockdown» gemäss der landesspezifischen Restriktionen eingeteilt. Die Erhebung umfasste demographische, klinische und histopathologische Daten. Zusätzlich wurde für eine gesonderte Analyse von «high-risk individuals» die persönliche und familiäre Melanomvorgeschichte und der Status der Behandlung mit Immunsuppression dokumentiert.

Die Studie wurde von der Kantonalen Ethikkommission Zürich genehmigt. Die Ethiknummer lautet 2014-0193.

Resultate

In den Referenzzentren reduzierte sich die Anzahl der Melanomdiagnosen länderübergreifend während der Lockdowns. Die Anzahl der Neudiagnosen erhöhte sich zwar wieder in der post-COVID-19-Periode, blieb jedoch unter dem Level vor COVID-19.

Eine signifikante Zunahme der Breslow-Tumordicke (Median 1.02 mm vs. 1.25 mm, $p < 0.001$) konnte während der post-COVID-19-Periode beobachtet werden. Besonders ausgeprägt war diese Zunahme in Italien, in Süddeutschland und in Österreich, wohingegen die Schweiz und Westdeutschland weniger betroffen waren. Im Weiteren zeigte sich eine signifikante Zunahme bei der Anzahl T3-T4-Melanome, der Ulzerationsrate und der Melanome mit einer Mitoserate von ≥ 2 (für alle, $p < 0.001$).

Die Überweisungen der Patienten durch Dermatologen an die Referenzzentren nahmen in der post-COVID-19-Periode zu ($p < 0.001$). Ebenfalls unterschieden sich die Melanom-Subtypen ($p = 0.001$). Während in beiden Perioden das Superfizielle Spreitende Melanom dominierte, erhöhte sich post-COVID-19 die Anzahl der Lentigo Maligna Melanome und der Nodulären Melanome.

Das Alter bei der Melanomdiagnose ($p < 0.01$) sowie eine positive Melanomvorgeschichte ($p < 0.01$) resultierten in der multivariaten Analyse in einer signifikanten Differenz der Breslow-Tumordicke. Hingegen zeigte sich bei den «high-risk individuals» mit einer aktiven Immunsuppression und einer positiven Melanomvorgeschichte eine Reduktion der log10 transformierten Breslow-Tumordicke während und nach dem Lockdown.

Schlussfolgerungen

Die Restriktionen während der COVID-19-Lockdowns resultierten in einer verzögerten Diagnose bzw. einem fortgeschritteneren Stadium des Melanoms bei der Erstdiagnose. Dabei korrelieren die höhere Breslow-Tumordicke, die Ulzeration und die Mitoserate stark mit dem Risiko der Metastasierung. Ältere Personen und Patienten mit einer positiven Melanomvorgeschichte zeigten sich besonders zögerlich bei der Wiederaufnahme regulärer Hautkrebsuntersuchungen.

Die Wichtigkeit regulärer Hautscreenings ist unbestritten. Der beobachtete Unterbruch in der Hautkrebsvorsorge könnte daher in der Zukunft mit einer höheren Mortalität und steigenden Gesundheitskosten einhergehen. Für eine abschliessende Beurteilung sind jedoch weitere Studien notwendig.

2. Eigenleistung

Der Startpunkt der Masterarbeit war die Datenrecherche und der daraus selbst erarbeitete Vorschlag eines Studiendesigns. Das Studiendesign wurde zusammen mit der Betreuerin finalisiert und enthielt folgende Parameter: Patienten-ID, Geschlecht, Geburtsdatum, Diagnosedatum, Alter bei der Diagnose, Zeitintervall zwischen dem Verdacht eines Melanoms und der histologisch gesicherten Melanomdiagnose, Körperstelle des Melanoms, Melanom-Typ, Breslow-Tumordicke, T-Stadium, Ulzeration, Mitoserate, Zuweiser an das Universitätsspital Zürich, persönliche Melanomvorgeschichte, familiäre Melanombelastung und aktive Immunsuppression.

Die Studienpopulation des Universitätsspitals Zürich wurde durch einen Auszug des Krebsregisters für den gewählten Studienzeitraum definiert. Der Auszug enthielt bereits einige Informationen zu den oben erwähnten Parametern. Insgesamt habe ich 785 Patienten- und histologische Berichte im Klinikinformationssystem studiert, den Auszug des Krebsregisters auf Korrektheit überprüft und die fehlenden Parameter ergänzt. Nach erfolgter Kontaktaufnahme und Einladung weiterer dermatologischer Referenzzentren war ich für die Koordination und das Zusammentragen der Daten aus insgesamt vier weiteren Kliniken verantwortlich. Schlussendlich wurden 7865 Melanomdiagnosen aus fünf verschiedenen Kliniken in einer Excel-Tabelle zusammengetragen, welche als Grundlage für die statistische Auswertung diente. Das Zusammentragen der Daten dauerte zirka ein Jahr.

Das Manuskript erarbeitete ich in Zusammenarbeit mit Dr. med. Florentia Dimitriou. Die statistische Auswertung erfolgte durch den Biostatistiker Patrick Turko.

Das Paper wird voraussichtlich im Journal of the European Academy of Dermatology and Venereology publiziert.

3. Paper

The impact of the COVID-19 pandemic on the diagnosis of cutaneous melanomas; a retrospective cohort study from five European skin cancer reference centers

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Abstract

Background

The COVID-19 lockdown had a dramatic impact on primary care access and resulted in postponed skin cancer screenings. This raises concerns for a diagnostic delay on primary cutaneous melanomas, which can subsequently increase morbidity and mortality.

Objectives

The aim of the study was to investigate the impact of the COVID-19-related restrictions on the melanoma diagnosis in five European skin cancer reference centers in Switzerland, Germany, Austria and Italy.

Methods

A total of 7865 cutaneous melanoma cases were collected between September 01, 2018 and August 31, 2021. The time period was stratified into pre-COVID (pre-lockdown) and post-COVID (lockdown and post-lockdown) according to the established restrictions in each country. The data collection included demographic, clinical and histopathological data from histologically confirmed cutaneous melanomas. Personal and family history of melanoma, as well as presence of immunosuppression were used to assess the diagnosis delay in high-risk individuals.

Results

There was an overall increase of the Breslow tumor thickness (mean 1.25 mm vs. 1.02mm) during the post-COVID period, as well as an increase in the proportion of T3-T4 melanomas, rates of ulceration and the number of mitotic rates ≥ 2 (all, $p < 0.001$). Patients with immunosuppression and personal history of melanoma showed a decrease in the mean log10-transformed Breslow during lockdown and post-COVID. In the multivariate analysis, age at melanoma diagnosis ($p < 0.01$) and personal history of melanoma ($p < 0.01$) showed significant differences in the mean Breslow thickness.

Conclusions

The study confirms the diagnostic delay in cutaneous melanomas due to the COVID-19 lockdown. High-risk individuals, such as patients with personal history of melanoma and elderly individuals, were more hesitant to restart their regular skin cancer screenings post-COVID. Further studies with longer follow-up are required to evaluate the consequences of this diagnostic delay in long-term outcomes.

Introduction

Cutaneous melanoma has a continuously increasing incidence and mortality in Europe, although mortality increases at a slower rate than incidence[1,2]. Between 1995 and 2012, the average annual percent change (AAPC) of invasive melanomas has been reported at 4% in men and 3% in women[3]. Despite the introduction of novel treatment agents, advanced melanoma remains the leading cause of death from skin cancer. Early diagnosis and management are essential for melanoma-specific survival, considering that melanoma has a predisposition for local invasive growth and metastatic spread[4]. The Breslow thickness, the presence of tumor ulceration as well as the mitotic rate are important factors that determine prognosis, and increasing Breslow thickness correlates with higher risk of metastatic spread[5]. For this reason, various measures have been taken to prevent melanoma and to diagnose it at an early stage.

As of March 2020, and following the declaration of the coronavirus disease 2019 (COVID-19) as pandemic, many European countries have declared restrictions and lockdowns to limit the COVID-19 dissemination, during which the citizens were urged to stay at home. Several hospitals, including skin cancer referral centers, had to be re-organized and routine medical and surgical activities had to be postponed[6]. The reduced level of access to medical care has led to extensive disruptions of primary cancer care; it is estimated that during the COVID-19 pandemic, i.e between January 2020 and April 2020, screenings for cancers of the breast, colon and cervix have dropped by 94%, 86% and 94%, respectively[7]. In skin cancer prevention, several retrospective studies suggest a decrease in diagnoses of thin melanomas and an increase of thick primary tumors after the COVID-19 lockdown, which raises concerns primarily about increased morbidity and mortality, and secondarily about increased health care costs[8-11]. Besides, although teledermatology has been implemented and facilitated assistance for several dermatological diseases during the COVID-19 pandemic, the diagnostic accuracy of dermoscopy is higher than teledermoscopy and the latter cannot replace face-to-face consultations[12].

Following these concerns for potential diagnostic delay in melanoma due to the applied COVID-19 pandemic-related restrictions, the EADV Melanoma Task Force has published a position statement that in individuals without prior history of skin cancer, clinical examination may be postponed for a maximum of 2-3 months and patients should be highly encouraged to perform regular self-examinations[13]. As diagnostic delay may be associated with a poor prognosis in melanoma, there is a need to underline the consequences of the COVID-19 pandemic on cutaneous melanoma diagnosis and increase awareness in the dermatologic community and health-care providers. In the present study, we sought to investigate the impact of the COVID-19-related restrictions on melanoma diagnosis in five European skin cancer reference centers, by comparing the mean numbers and the histopathological characteristics of new cutaneous melanomas diagnosed before, during and after the COVID-19-related lockdown period.

Methods

Study population and data collection

Demographic, clinical and histopathological data from histologically confirmed cutaneous melanomas between September 01, 2018 and August 31, 2021 were retrospectively collected from five European skin cancer reference centers in Switzerland, Germany, Austria and Italy. As post-COVID-19 period, we defined the time from the first confirmed COVID-19 diagnosis in each country to August, 31, 2021 (data cut-off), thereafter referred as “post-COVID”. For the data analysis, the post-COVID period was stratified into “lockdown” and “post-lockdown”, according to the established restrictions in each European country[14]. The lockdown period was defined as the period encompassing stay-at-home orders, curfews, quarantines, cordons *sanitaries* and similar societal restrictions[14]. The corresponding time period before the first COVID-19 case was equally assessed and compared with the number of new cutaneous melanomas prior to the COVID-19 pandemic (pre-COVID-19 period, thereafter referred as “pre-COVID” or “pre-lockdown”). Lesions with non-definitive diagnosis and melanomas of unknown primary site were excluded. Data were retrieved from the institutional skin cancer registries and histopathology data banks. The data collection included patient age, sex, date of birth, date of diagnosis, anatomic location and subtype of the cutaneous melanoma, tumor Breslow thickness, presence of ulceration, mitotic rate, type of referral (dermatologist, family doctor, self-referral etc), personal and family history of melanoma and presence of immunosuppression. Notably, *in situ* melanomas are not routinely documented in the Swiss database. The primary endpoint of the study was to investigate the mean number of cutaneous melanomas and to assess the difference of the mean Breslow thickness before and during the COVID-19 pandemic. The secondary objectives were: 1) to assess the difference of other primary histological characteristics, such as ulceration and mitotic rate, for the above mentioned time periods; 2) to investigate the proportion of *in situ* melanomas and 3) to assess the diagnosis delay in high-risk individuals, including those with prior history of skin cancer, family history of melanoma and immunosuppressive treatment.

Statistical analysis

Cases were stratified into pre- and post- COVID, and summary statistics were calculated comparing these two time periods. Differences between the mean values of continuous variables in each time period were tested using Student's t-tests, and Fisher's exact test was used to test proportional differences between categorical variables. This procedure was performed separately for characteristics relating to the study population and the set of melanoma primaries, and in each case *p*-values were adjusted using Bonferroni's correction. Further univariate and multivariate tests were performed on log-10 transformed data using linear models. As these linear models include a large amount of data (5000+ points), statistical significance can be reached for even very small differences. We therefore also report adjusted R-squared and a measure of effect size for each model. All statistical tests were performed using R version 4.2[15]. Effect sizes were calculated using the package "effect size" version 0.7.0[16].

Results

Study population characteristics

A total of 7865 cutaneous melanoma cases were included in the final analysis; 4340 (55%) were diagnosed during the pre-COVID period and 3525 (45%) in the post-COVID period. The study population characteristics are summarized in **Table 1**. Overall, median age at melanoma diagnosis was 63 years (range 7-103 years) and 64.5 years (range 13-101 years) in the pre- and post-COVID period, respectively ($p = 0.01$), 2302 (53%) and 1866 (53%) patients were male ($p = 0.94$). Among the primaries for which the body site was known (n = 4194), trunk and lower extremities were the most common body sites ($p = 0.22$). The cutaneous melanoma subtype differed significantly ($p = 0.001$); the proportion of nodular melanomas (NM) (7% vs 9%) and lentigo maligna melanomas (LMM) (7% vs 10%) increased post-COVID although superficial spreading melanoma (SSM) was the most common melanoma subtype pre- and post-COVID. The type of referral showed numerical differences between the pre-COVID and the post-COVID period with 491 (11%) and 1181 (34%) of the cases, respectively, being referred from a dermatologist ($p < 0.001$). The proportions of the patients with personal ($p = 0.91$) and family history of melanoma ($p = 0.001$) was equally distributed between the two time periods.

Cutaneous melanoma characteristics

Invasive cutaneous melanomas diagnosed during the post-COVID period had a higher average Breslow tumor thickness [mean 1.25 mm, SD 2.51, median 0.5 mm (range 0-50mm)] compared to those diagnosed in the pre-COVID period [mean 1.02 mm, SD 1.91, median 0.4 mm (range 0-28mm)] ($p < 0.001$). This trend was also observed in the cutaneous melanoma thickness categorized according to the T stage; there were proportionally more T3-T4 melanomas during the post-COVID period, compared to the pre-COVID period (617, 18% vs. 605, 14%; $p < 0.001$). Similarly, the proportion of *in situ* melanomas reduced during the post-COVID period (1637, 38% vs. 1219, 35%). Among the cutaneous melanomas diagnosed during the post-COVID period, the rates of ulceration increased (457, 13% vs. 415, 10%; $p < 0.001$). In addition, among the 1119 primary lesions with reported mitotic rate, the number of cutaneous melanomas with a mitotic rate ≥2 significantly increased after COVID-19 (271, 8% vs. 162, 4%; $p < 0.001$). Overall, there was a reported diagnosis delay of more than eight weeks from the discovery of the suspicious lesion to the melanoma diagnosis in 266 (8%) of the cases diagnosed during the post-COVID period. The respective number in the pre-COVID period was 256 (6%) cases, but the difference was not significant ($p = 0.3$). A summary of the melanoma primary characteristics is presented in **Table 2**.

Breslow thickness and T stage

The mean values of the log10-transformed Breslow thickness showed significant differences during the pre- and the post-COVID period ($p < 0.01$) (**Figure 1**). Analyzed by country site, there was an overall increase of the log10-transformed Breslow thickness during the lockdown and the post-

COVID period in Italy, South Germany and Austria, with a statistically significant difference in Austria ($p < 0.01$) (**Figure 2**). In Switzerland, the log10 transformed Breslow decreased during the lockdown period, with a subsequent increase after lockdown. A converse trend was observed in West Germany, where the log10-transformed Breslow increased during lockdown and decreased post-COVID.

The proportion of T3-T4 melanomas increased during the post-COVID period in the overall study population (**Table 2,** $p < 0.001$). This summary was also apparent in time series data for the whole population (**Figure 3**) and for each country separately (**Figure 4**). The number of cutaneous melanomas for each T stage in the overall study population and by site are summarized in the supplementary material, *available online*.

Breslow thickness in high-risk individuals

Presence of immunosuppression, as well as personal and family history of melanoma are known risk factors for a subsequent melanoma diagnosis. We compared the Breslow thickness for the two time periods in these high-risk individuals. Out of the 3919 patients with available personal history information, 448 (11%) patients reported a previous melanoma diagnosis. In the patients with invasive cutaneous melanomas and positive personal history, the mean log10-transformed Breslow thickness numerically decreased during the lockdown and the post-COVID period (**Figure 5**). Similarly, 38 (2%) out of 1603 patients with known immunosuppression status, active immunosuppression and invasive cutaneous melanomas, showed a decrease in the mean log10-transformed Breslow during lockdown and post-COVID, although the numbers were too small to draw any statistical conclusions (supplementary material, *available online*). Family history of melanoma was reported in 144 (5%) out of 2858 patients; in the patients with invasive cutaneous melanomas, the mean log10-transformed Breslow thickness increased during the lockdown and post-COVID (**Figure 6**).

Univariate and multivariate analysis

Separate linear models were fit to compare the effect of selected variables, including age at cutaneous melanoma diagnosis, sex, personal or family history of melanoma and presence of immunosuppression, on the mean log10-transformed Breslow thickness in univariate analyses. These models revealed no statistically significant difference in the mean Breslow thickness between the age of cutaneous melanoma diagnosis ($p = 0.78$), family history of melanoma ($p = 0.08$), or presence of immunosuppression ($p = 0.88$). Nevertheless, sex ($p < 0.01$), personal history of melanoma ($p < 0.01$) and the COVID-19 period ($p < 0.01$) met statistical significance, although they separately explained only small amounts of the variation (R^2 for sex = 0.003, melanoma history = 0.04, COVID-19 = 0.003). The standardized effect sizes of these variables (Cohen's *d*) were 0.11 for sex, 0.66 for melanoma history, and 0.11 for the COVID-19 period, which we interpret as "small" for sex and COVID-19, and "medium" sized effect for melanoma history[17].

A multivariate model was fit to express Breslow thickness as additive function of age, sex, personal history of melanoma, family history of melanoma, immunosuppression and COVID-19 period. The overall model p-value ($p < 10^{-16}$) and adjusted R^2 (0.07) showed a better fit than the individual models. In the multivariable analysis, however, only age at cutaneous melanoma diagnosis ($p < 0.01$) and personal history of melanoma ($p < 0.01$) showed significant differences in the mean Breslow thickness, and the effect of these differences was small ($d = 0.19$ for age; $d = 0.55$ for melanoma history).

Discussion

We report the results of a retrospective, multicenter study, investigating the impact of the COVID-19-related restrictions on cutaneous melanoma diagnosis in five European skin cancer reference centers. Similar to the reported data in other cancers[18,19], we document a significant reduction in the number of new melanoma diagnoses during the lockdown period, which increased again in the period immediately after the first strict COVID-19 lockdown and while patients were constantly rescheduled to attend skin cancer screening visits. Further suggested from other studies[9,20-22], we confirm that many patients experienced a delay in the melanoma diagnosis during the lockdown period. Notably, there was a diagnosis delay of ≥ 8 weeks from the discovery of the suspicious cutaneous lesion to the melanoma diagnosis in 8% of the cases diagnosed during the post-COVID period. This diagnosis delay resulted in cutaneous melanomas with higher mean Breslow thickness, higher mitotic rate and commonly presence of ulceration during the post-COVID period. Despite the subsequent increase in the number of diagnoses after the COVID-19 lockdown, high-risk individuals, such as patients with personal history of melanoma and elderly individuals were probably hesitant to restart their regular skin cancer screenings, as suggested by the higher mean Breslow thickness in the multivariable analysis. This delay in the melanoma diagnosis in these patient subgroups may therefore pose a substantial risk for increased morbidity and mortality.

Compared to the pre-COVID period, there was an overall decrease in the number of new cases diagnosed after the COVID-19 lockdown, which can be partially explained by maintained disruptions in the regular skin cancer screenings, due to subsequent short-period lockdowns, or even patient hesitancy due to fear of contamination by visiting the hospital. This observation is further confirmed from other retrospective studies[9,20-22]. Contradictory, no difference was reported in a study from Southern Italy[23] and in a nationwide histopathology registry in the Netherlands, the 3-week average of the number of melanomas diagnosed after the second lockdown even increased in number[24]. When analyzed according to the country site, the mean Breslow thickness increased during the post-COVID period, which subsequently led to an increase in the number of T3 and T4 cutaneous melanomas. This observation was particularly evident in Italy, South Germany and Austria, whereas Switzerland and West Germany were less affected. Indeed, the COVID-19 restrictions in Europe showed relevant regional differences, with Italy enforcing more urgent restrictions compared to Germany, Switzerland and Austria.

Early melanoma diagnosis is crucial for the survival of patients and several studies conducted during the COVID-19 period have underlined the diagnostic delay in melanoma and other cancers[7]. In

the current study, the impact of the COVID-19 pandemic on the regular skin cancer screening resulted in a greater proportion of melanomas being diagnosed at a more advanced T stage. It is well known that the risk of metastases increases with the increase of the Breslow thickness and that tumor ulceration and mitotic rate correlate with the risk of metastatic spread[5]. Similarly, the number of NM and LMM increased in the period following the COVID-19 lockdown, and this observation is further suggestive of a diagnosis delay. NM is associated with a worse outcome compared to SSM[25] and LMM typically derives from a chronic sun damaged skin and demonstrates a slow growing, lentiginous growth pattern[26]. We hypothesize that this diagnosis delay may have a potential impact on future morbidity, mortality and might generate healthcare costs, although the patient outcome was not an objective of this study.

Overall, the onset of the COVID-19 pandemic has interrupted the regular skin cancer screening. In spite of several recommendations from the dermatologic community to restart skin checks, the effectiveness of the existing skin cancer prevention programs, in particular with regard to an over-diagnosis, has been controversially discussed, with several studies suggesting a reassessment. Indeed, the incidence of cutaneous melanoma has substantially increased in the last years in the USA[27] and in Europe[1] with some investigators suggesting an “epidemic of diagnosis”[28]. This assumption is further supported by an analysis of the relative change in the incidence of cutaneous and non-cutaneous melanoma in the USA from 1975 through 2017, indicating a rise in cutaneous melanoma diagnoses, whereas the incidence of non-cutaneous melanoma has remained stable. This might indicate a trend for an over-diagnosis in cutaneous melanoma, which is probably a result of a combined effect of a significant increase in screening skin examinations, increase in the number of biopsies of pigmented nevi and low pathological threshold to label suspicious morphological changes as melanomas. Further supported by the lack of an apparent effect on mortality, some dermatologists and epidemiologists advice against restarting a population-wide screening after the COVID-19 pandemic.

On the other hand, delays in the melanoma diagnosis may have a profound impact on melanoma-associated survival and thus far, stable mortality has been considered as a success of the established screening programs. In the current study, there was a substantial increase in the number of melanomas referred directly from a dermatologist during the post-COVID period. This trend underlines the high awareness in the dermatologic community concerning the melanoma diagnosis delay during the COVID-19 pandemic. In line with this perspective, the EADV task force declared that the excision of a suspicious lesion should be performed within short time from the initial discovery[29]. The urgency of early diagnosis can be additionally supported by the fact that thin invasive melanomas, which account for a fourth of the cutaneous melanomas and the majority of deaths in Australia[30], should not be underestimated. Conversely, the substantial decrease in the number of new melanoma diagnoses during the COVID-19, with an increase in the histological features that suggest high proliferation and therefore, higher risk for metastatic spread, indicate that the need for restarting the screening activities is compulsory. An increased cooperation between clinician-dermatologists and histopathologists is crucial in the diagnostic process to increase diagnostic accuracy and decrease over- or underdiagnosis.

In all, this study confirms the diagnostic delay of cutaneous melanomas as an impact of the COVID-19 pandemic. Ultimately, although patients` outcome was not in the scope of the current study,

it is expected that this diagnosis delay may subsequently increase patients` morbidity and mortality, as well as the healthcare-associated costs in the next years. Specific patient subpopulations might be more prone to this diagnostic delay and continuous monitoring of these populations is crucial. These data highlight the importance to reinforce skin cancer prevention activities, in order to maintain skin cancer care. Further studies with longer follow-up will allow for a more accurate evaluation of this diagnostic delay in long-term outcomes.

Conflicts of interest

FD receives/received honoraria and travel support from Merck Sharp & Dohme, Bristol Myers Squibb and Sun Pharma.

RD declares intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, Alligator, T3 Pharma, MaxiVAX SA and touchIME outside the submitted work.

GL has received travel support from Sun Pharma.

EL received honoraria from Novartis, Medac, Bristol Myers Squibb, Sanofi, Sun Pharma, and Pierre Fabre, reports consulting/advisory roles with Bristol Myers Squibb, Pierre Fabre and Novartis; and received travel/accommodations/expenses from Pierre Fabre, Bristol Myers Squibb, Medac, and Sun Pharma.

All other authors have declared no conflicts of interest.

Authors' contributions: Study concept: FD, RD. Study design: FD, AT. Data acquisition: AT, HM, SF, KP, GL, PFC. Quality control of data and algorithms: FD, AT. Data analysis and interpretation: FD, AT. Statistical analysis: PT. Manuscript preparation: FD, AT. Manuscript editing: FD, AT. All authors revised the manuscript and approved the submission. All authors had full access to all the data and the final responsibility to submit for publication.

Ethics approval and consent to participate: The study was approved by the local institutional ethics review boards.

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Figure Legends

Figure 1. Smoothed log10-transformed Breslow thickness between September 01, 2018 and August 31, 2021 (A) and mean values during the pre- and the post-COVID period (B) for the study population.

Figure 2. Smoothed log10-transformed Breslow thickness between September 01, 2018 and August 31, 2021 (A) and mean values during the pre- and the post-COVID period (B) for each site.

Abbreviations: RM; Rome (Italy), SALK; Salzburg (Austria), Tübingen; Tuebingen (Germany), UK Essen; Essen (Germany), ZRH; Zurich (Switzerland)

Figure 3. T-stage of the primary melanomas diagnosed monthly, shown by the raw count over time (A) and by the fraction of lesions (B)**.**

Figure 4. T-stage of the primary melanomas diagnosed monthly, shown by the raw count over time (A) and by the fraction of lesions (B) for each site.

Abbreviations: RM; Rome (Italy), SALK; Salzburg (Austria), Tübingen; Tuebingen (Germany), UK Essen; Essen (Germany), ZRH; Zurich (Switzerland)

Figure 5. Mean log10-transformed Breslow thickness post-COVID, during lockdown and pre-COVID, in patients with invasive primary melanomas and positive personal history.

Figure 6. Mean log10-transformed Breslow thickness post-COVID, during lockdown and pre-COVID, in patients with invasive primary melanomas and positive family history.

Supplementary Material

Figure S1. T-stage of the primary melanomas diagnosed during the pre- and post-COVID period, shown by the raw count (A) and by the fraction of lesions (B).

Figure S2. T-stage of the primary melanomas diagnosed during the pre- and post-COVID period, shown by the raw count (A) and by the fraction of lesions (B) for each site.

Abbreviations: RM; Rome (Italy), SALK; Salzburg (Austria), Tübingen; Tuebingen (Germany), UK Essen; Essen (Germany), ZRH; Zurich (Switzerland)

Figure S3. Mean log10-transformed Breslow thickness post-COVID, during lockdown and pre-COVID, in patients with invasive primary melanomas and active immunosuppression.

References

1. Forsea AM: Melanoma Epidemiology and Early Detection in Europe: Diversity and Disparities. Dermatol Pract Concept 10:e2020033, 2020
2. Dimitriou F, Krattinger R, Ramelyte E, et al: The World of Melanoma: Epidemiologic, Genetic, and Anatomic Differences of Melanoma Across the Globe. Curr Oncol Rep 20:87, 2018
3. Sacchetto L, Zanetti R, Comber H, et al: Trends in incidence of thick, thin and in situ melanoma in Europe. Eur J Cancer 92:108-118, 2018
4. Liu W, Dowling JP, Murray WK, et al: Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. Arch Dermatol 142:1551-8, 2006
5. Gershenwald JE, Scolyer RA: Melanoma Staging: American Joint Committee on Cancer (AJCC) 8th Edition and Beyond. Ann Surg Oncol 25:2105-2110, 2018
6. O'Reilly-Shah VN, Van Cleve W, Long DR, et al: Impact of COVID-19 response on global surgical volumes: an ongoing observational study. Bull World Health Organ 98:671-682, 2020
7. Preventive cancer screenings during COVID-19 pandemic. Epic Health Research Network. 2020. [2020-09-01]. https://ehrn.org/articles/delays-in-preventive-cancer-screenings-during-covid-19-pandemic.
8. Ricci F, Fania L, Paradisi A, et al: Delayed melanoma diagnosis in the COVID-19 era: increased breslow thickness in primary melanomas seen after the COVID-19 lockdown. J Eur Acad Dermatol Venereol 34:e778-e779, 2020
9. Hoellwerth M, Kaiser A, Emberger M, et al: COVID-19-Induced Reduction in Primary Melanoma Diagnoses: Experience from a Dermatopathology Referral Center. J Clin Med 10, 2021
10. Marson JW, Maner BS, Harding TP, et al: The magnitude of COVID-19's effect on the timely management of melanoma and nonmelanoma skin cancers. J Am Acad Dermatol 84:1100-1103, 2021
11. Andrew TW, Alrawi M, Lovat P: Reduction in skin cancer diagnoses in the UK during the COVID-19 pandemic. Clin Exp Dermatol 46:145-146, 2021
12. Chuchu N, Dinnes J, Takwoingi Y, et al: Teledermatology for diagnosing skin cancer in adults. Cochrane Database Syst Rev 12:CD013193, 2018
13. Dessinioti C, Garbe C, Stratigos AJ: The impact of the COVID-19 pandemic on diagnostic delay of skin cancer: a call to restart screening activities. J Eur Acad Dermatol Venereol 35:e836-e837, 2021
14. Wikipedia. COVID-19 Lockdowns. Available online: https://en.wikipedia.org/wiki/COVID-19_lockdowns#Table_of_pandemic_lockdown.
15. R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing V, Austria. URL https://www.R-project.org/.
16. Ben-Shachar M LD, Makowski D (2020). Estimation of Effect Size Indices and Standardized Parameters. Journal of Open Source Software, 5(56), 2815
17. Cohen J: Statistical Power Analysis for the Behavioral Sciences, 2nd Ed. New York: Routledge.
18. Maringe C, Spicer J, Morris M, et al: The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol 21:1023-1034, 2020
19. Vissio E, Falco EC, Collemi G, et al: Impact of COVID-19 lockdown measures on oncological surgical activity: Analysis of the surgical pathology caseload of a tertiary referral hospital in Northwestern Italy. J Surg Oncol 123:24-31, 2021
20. Gualdi G, Porreca A, Amoruso GF, et al: The Effect of the COVID-19 Lockdown on Melanoma Diagnosis in Italy. Clin Dermatol 39:911-919, 2021
21. Molinier R, Roger A, Genet B, et al: Impact of the French COVID-19 pandemic lockdown on newly diagnosed melanoma delay and severity. J Eur Acad Dermatol Venereol 36:e164-e166, 2022
22. Scharf C, Brancaccio G, Di Stefani A, et al: The association between COVID-19 lockdowns and melanoma diagnosis and thickness: A multicenter retrospective study from Europe. J Am Acad Dermatol 87:648-649, 2022
23. Ruggiero A, Martora F, Fornaro F, et al: Reply to 'Impact of the French COVID-19 pandemic lockdown on newly diagnosed melanoma delay and severity' by R. Molinier et al. J Eur Acad Dermatol Venereol, 2022
24. Sangers TE, Wakkee M, Kramer-Noels EC, et al: Limited impact of COVID-19-related diagnostic delay on cutaneous melanoma and squamous cell carcinoma tumour characteristics: a nationwide pathology registry analysis. Br J Dermatol 187:196-202, 2022

25. Lattanzi M, Lee Y, Simpson D, et al: Primary Melanoma Histologic Subtype: Impact on Survival and Response to Therapy. J Natl Cancer Inst 111:180-188, 2019
26. Whiteman DC, Pavan WJ, Bastian BC: The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res 24:879-97, 2011
27. National Cancer Institute. Cancer Statistics Review (CSR) 1975-2016 (https://seer.cancer.gov/csr/1975_2016/browse_csr.php?sectionSEL=1&pageSEL=sect_01_table.01. opens in new tab).
28. Welch HG, Mazer BL, Adamson AS: The Rapid Rise in Cutaneous Melanoma Diagnoses. N Engl J Med 384:72-79, 2021
29. Arenbergerova M, Lallas A, Nagore E, et al: Position statement of the EADV Melanoma Task Force on recommendations for the management of cutaneous melanoma patients during COVID-19. J Eur Acad Dermatol Venereol 35:e427-e428, 2021
30. Whiteman DC, Baade PD, Olsen CM: More people die from thin melanomas (1 mm) than from thick melanomas (>4 mm) in Queensland, Australia. J Invest Dermatol 135:1190-1193, 2015

Table 1. Study population characteristics

	Pre-Covid (N=4340)	Post-Covid (N=3525)	*P*-value[1]
Age at Diagnosis			
Mean (SD)	62.3 (16.2)	63.2 (15.6)	0.0157
Median [Min, Max]	63.0 [7.00, 103]	64.5 [13.0, 101]	
Sex			
Female	2038 (47%)	1659 (47%)	0.944
Male	2302 (53%)	1866 (53%)	
Melanoma body site			
Head & neck	435 (10%)	382 (11%)	0.223
Lower extremities	493 (11%)	446 (13%)	
Other	22 (0.5%)	14 (0.4%)	
Trunk	903 (21%)	728 (21%)	
Upper extremities	392 (9%)	379 (11%)	
Melanoma subtype			
ALM	78 (2%)	71 (2%)	0.00167
Desmoplastic melanoma	13 (0.3%)	17 (0.5%)	
Lentigo maligna	299 (7%)	355 (10%)	
Nodular	292 (7%)	307 (9%)	
Other	225 (5%)	205 (6%)	
SSM	1245 (29%)	1041 (30%)	
Referral			
Dermatologist	491 (11%)	1181 (34%)	<0.001
Family doctor	106 (2%)	132 (4%)	
Skin cancer prevention program	148 (3%)	103 (3%)	
Other	44 (1%)	25 (0.7%)	
Hospital	51 (1%)	71 (2%)	
Self-referral	163 (4%)	64 (2%)	
Melanoma personal history			
No	1853 (43%)	1618 (46%)	0.91
Yes	241 (6%)	207 (6%)	
Melanoma family history			
No	1676 (39%)	1038 (29%)	0.00124
Yes	69 (2%)	75 (2%)	

Abbreviations: ALM; acral lentiginous melanoma, SSM; superficial spreading melanoma.

Unknown cases have been excluded from the present analysis.

[1]Student's t-tests, and Fisher's exact test

Table 2. Primary melanoma characteristics

	Pre-Covid (N=4340)	Post-Covid (N=3525)	*P*-value[1]
Time from first discovery to histological diagnosis			
> 8 weeks	256 (6%)	266 (8%)	0.304
≤ 4 weeks	151 (4%)	147 (4%)	
4 - 8 weeks	50 (1%)	68 (2%)	
Breslow thickness			
Mean (SD)	1.02 (1.91)	1.25 (2.51)	<0.001
Median [Min, Max]	0.400 [0, 28.0]	0.500 [0, 50.0]	
T stage (AJCCv8)			
In situ	1637 (38%)	1219 (35%)	<0.001
T1	1470 (34%)	1174 (33%)	
T2	549 (13%)	465 (13%)	
T3	344 (8%)	335 (10%)	
T4	261 (6%)	282 (8%)	
Presence of ulceration			
No	3612 (83%)	2838 (81%)	<0.001
Yes	415 (10%)	457 (13%)	
Mitotic rate			
0 - 1	426 (10%)	260 (7%)	<0.001
2 - 3	83 (2%)	189 (5%)	
≥ 4	79 (2%)	82 (2%)	

Unknown cases have been excluded from the present analysis.

[1]Student's t-tests, and Fisher's exact test

Figure 1. Smoothed log10-transformed Breslow thickness between September 01, 2018 and August 31, 2021 (A) and mean values during the pre- and the post-COVID period (B) for the study population.

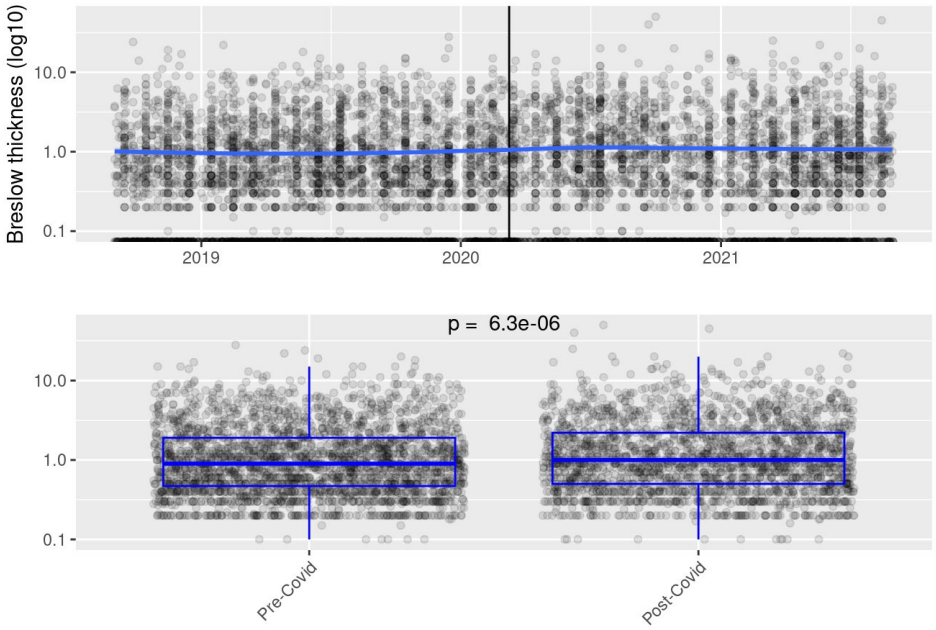


Figure 2. Smoothed log10-transformed Breslow thickness between September 01, 2018 and August 31, 2021 (A) and mean values during the pre- and the post-COVID period (B) for each site.

Abbreviations: RM; Rome (Italy), SALK; Salzburg (Austria), Tübingen; Tuebingen (Germany), UK Essen; Essen (Germany), ZRH; Zurich (Switzerland)

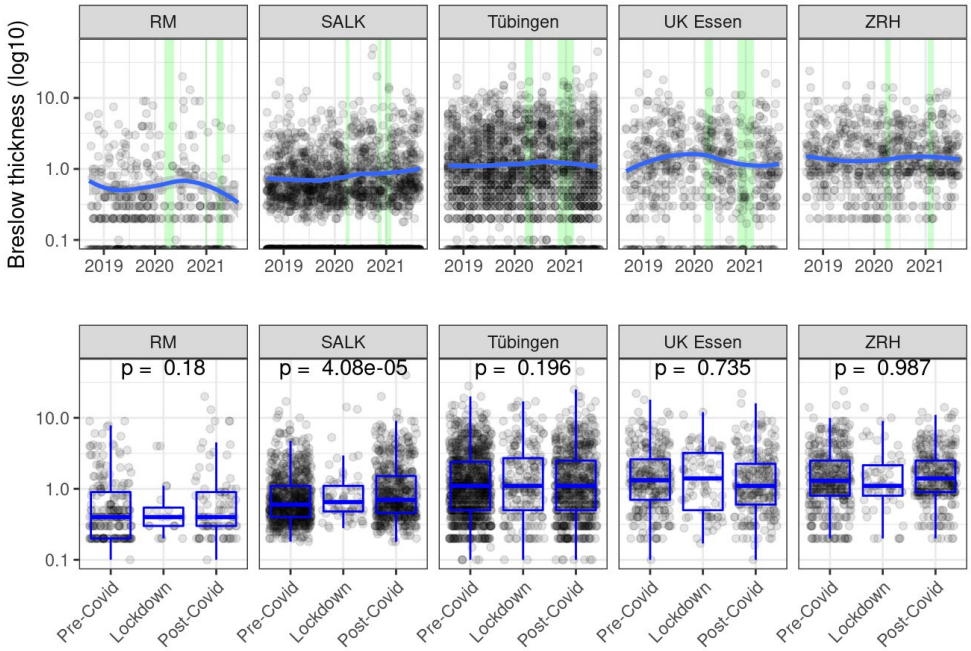


Figure 3. T-stage of the primary melanomas diagnosed monthly, shown by the raw count over time (A) and by the fraction of lesions (B).

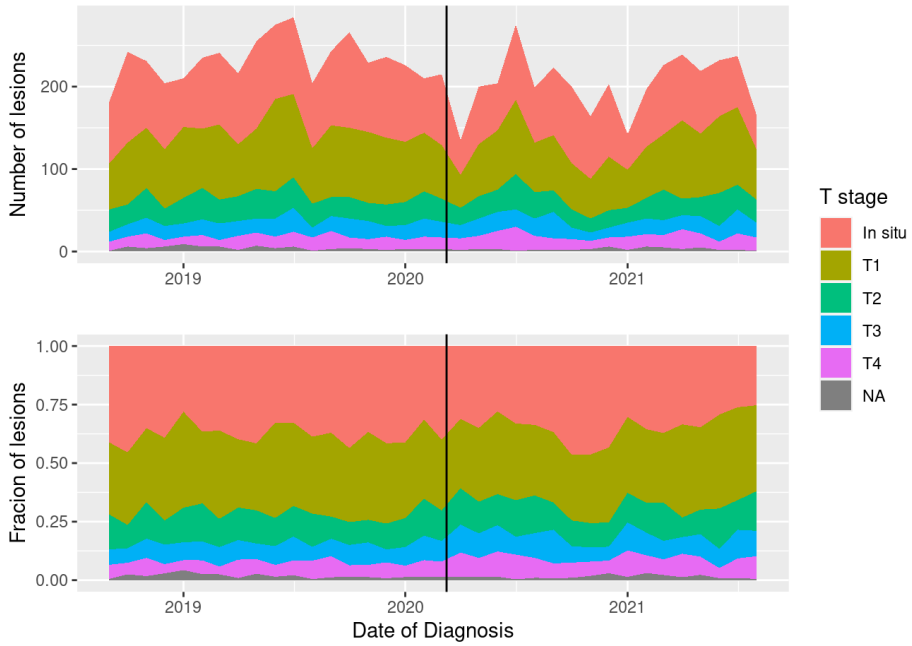


Figure 4. T-stage of the primary melanomas diagnosed monthly, shown by the raw count over time (A) and by the fraction of lesions (B) for each site.

Abbreviations: RM; Rome (Italy), SALK; Salzburg (Austria), Tübingen; Tuebingen (Germany), UK Essen; Essen (Germany), ZRH; Zurich (Switzerland)

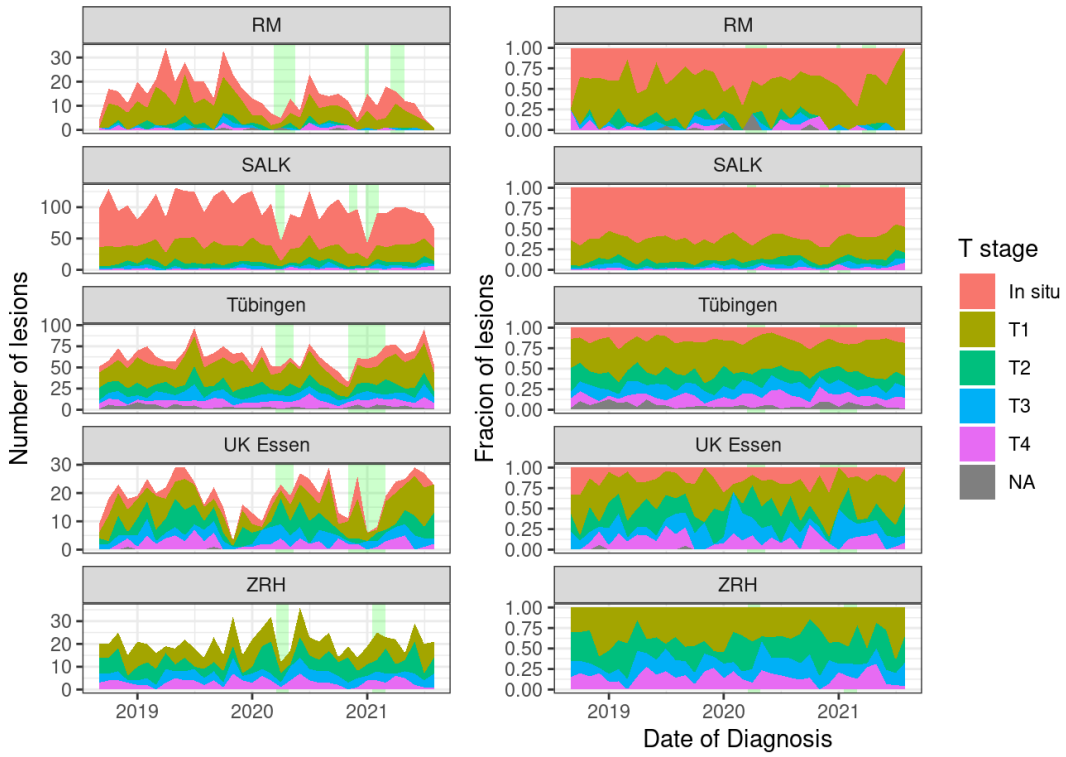
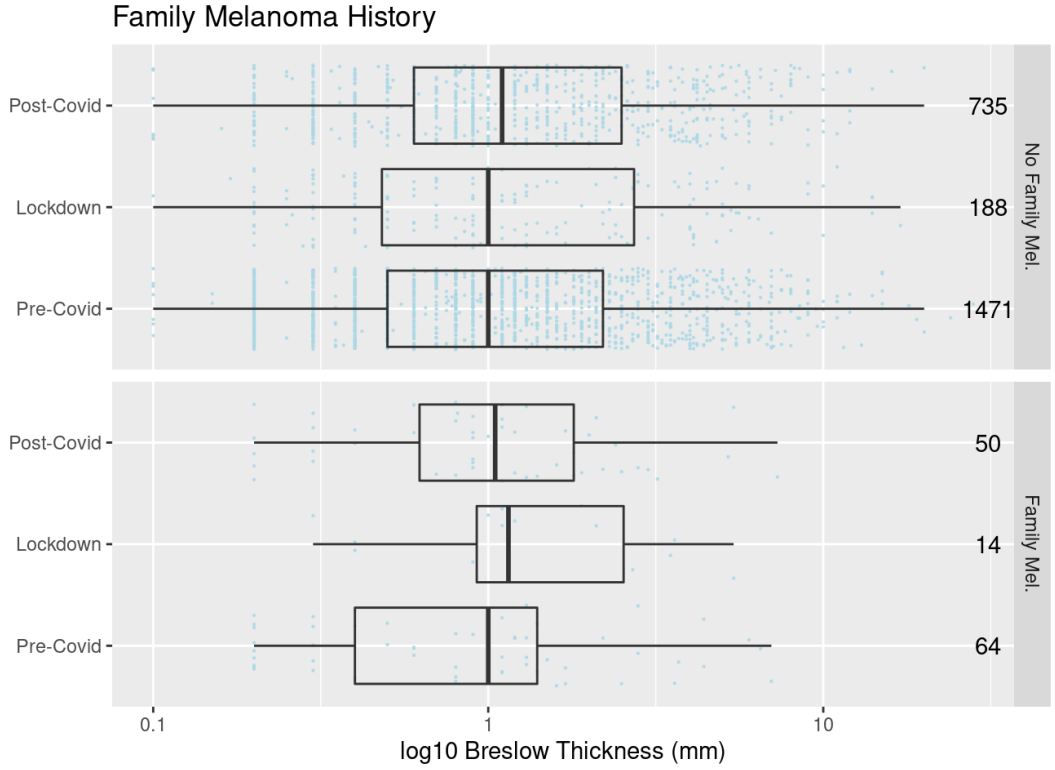


Figure 5. Mean log10-transformed Breslow thickness post-COVID, during lockdown and pre-COVID, in patients with invasive primary melanomas and positive personal history.

Figure 6. Mean log10-transformed Breslow thickness post-COVID, during lockdown and pre-COVID, in patients with invasive primary melanomas and positive family history.



Supplementary Material

Figure S1. T-stage of the primary melanomas diagnosed during the pre- and post-COVID period, shown by the raw count (A) and by the fraction of lesions (B).

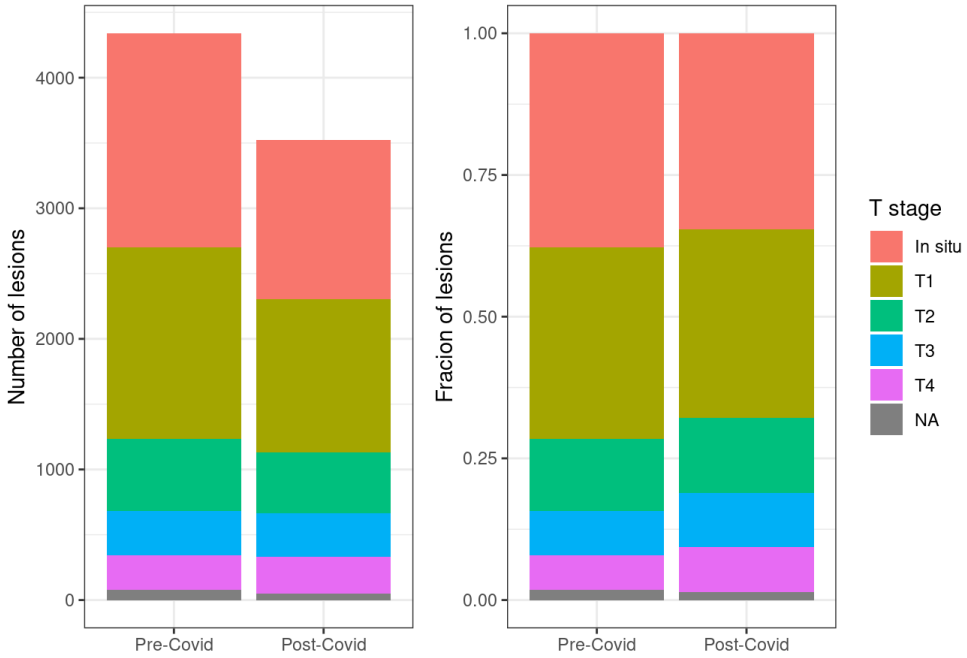


Figure S2. T-stage of the primary melanomas diagnosed during the pre- and post-COVID period, shown by the raw count (A) and by the fraction of lesions (B) for each site.

Abbreviations: RM; Rome (Italy), SALK; Salzburg (Austria), Tübingen; Tuebingen (Germany), UK Essen; Essen (Germany), ZRH; Zurich (Switzerland)

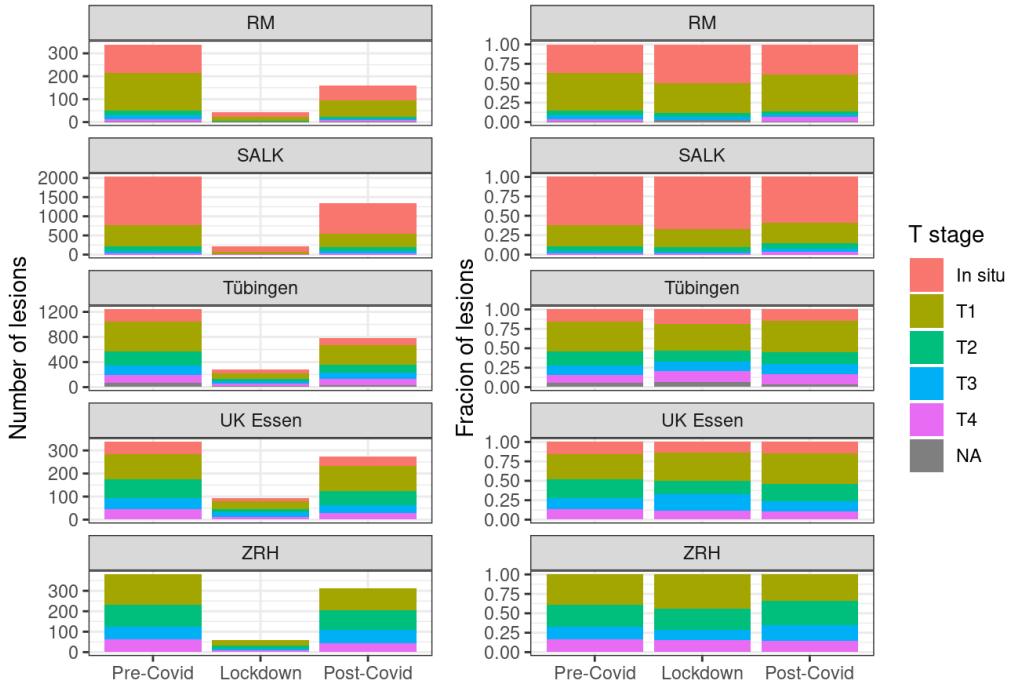
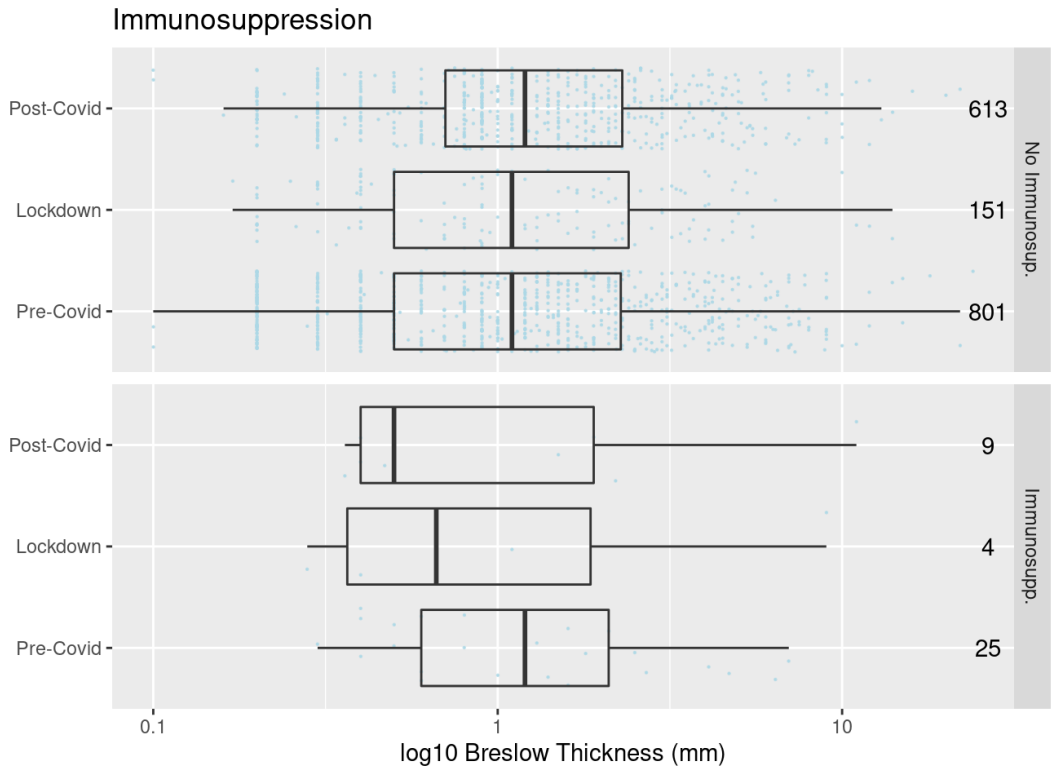


Figure S3. Mean log10-transformed Breslow thickness post-COVID, during lockdown and pre-COVID, in patients with invasive primary melanomas and active immunosuppression.



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4. Lebenslauf

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	Medizinstudium im Luzerner Track

5. Erklärung

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M Med UniLU UZH

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