# Limited impact of COVID-19-related diagnostic delay on cutaneous melanoma and squamous cell carcinoma tumour characteristics: a nationwide pathology registry analysis

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## Abstract

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Background The COVID-19 pandemic reduced the number of skin cancer diagnoses, potentially causing a progression to unfavourable tumour stages.
Objectives To identify the impact of delayed diagnostics on primary invasive melanoma and cutaneous squamous cell carcinoma (cSCC) by comparing tumour (pT) stage, Breslow thickness and invasion depth from before to after the first and second lockdown periods.
Methods In this population-based cohort study, histopathology reports registered between 1 January 2018 and 22 July 2021 were obtained from the nationwide histopathology registry in the Netherlands. The Breslow thickness of melanomas, invasion depth of cSCCs, and pT stage for both tumour types were compared across five time periods: (i) pre-COVID, (ii) first lockdown, (iii) between first and second lockdowns, (iv) second lockdown and (v) after second lockdown. Breslow thickness was compared using an independent t-test. pT-stage groups were compared using a $\chi^2$-test. Outcomes were corrected for multiple testing using the false discovery rate.
Results In total, 20 434 primary invasive melanomas and 68 832 cSCCs were included in this study. The mean primary melanoma Breslow thickness of the prepandemic era (period i) and the following time periods (ii–v) showed no significant difference. A small shift was found towards unfavourable pT stages during the first lockdown compared with the pre-COVID period: pT1 52·3% vs. 58·6%, pT2 18·9% vs. 17·8%, pT3 13·2% vs. 11·0%, pT4 9·1% vs. 7·3% (P = 0·001). No relevant changes were seen in subsequent periods. No significant change in pT stage distribution was observed between the pre-COVID (i) and COVID-affected periods (ii–v) for cSCCs.
Conclusions To date, the diagnostic delay caused by COVID-19 has not resulted in relatively more unfavourable primary tumour characteristics of melanoma or cSCC. Follow-up studies in the coming years are needed to identify a potential impact on staging distribution and survival in the long term.

The COVID-19 pandemic has had a tremendous impact globally on patients with cancer, including treatment delays and missed cancer diagnoses. In the Netherlands, the first case of COVID-19 was registered at the end of February 2020, and strict social distancing measures were implemented on 15 March 2020. Since the start of the pandemic, two nationwide

lockdowns have been implemented in the Netherlands, during 2020 and 2021, to prevent the spread of COVID-19.[1] Not only were population-based cancer screening programmes (e.g. for breast cancer) temporarily halted, but routine care was also downscaled.[2] Similarly to many other countries in Europe, the latter also severely constrained skin cancer care, resulting in a steep decline in melanoma and cutaneous squamous cell carcinomas (cSCCs) diagnoses. Although reporting of skin cancer has fortunately increased again, the rebound is thought to be incomplete, but most data still require additional adjustment for changed population age distributions.[3–9]

These nationwide reductions in skin cancer incidence offer a unique possibility to study the impact of diagnostic delay on skin cancer characteristics. Researchers have hypothesized that the delay of skin cancer diagnoses may have resulted in cases of skin cancer progressing to unfavourable cancer stages.[2,10] In line with this hypothesis, several small-scale studies have reported thicker melanomas being diagnosed during the COVID pandemic compared with the pre-COVID era.[11–14] In contrast, recent single-institution studies from the UK and Belgium found no impact of COVID-19-related delayed diagnoses on melanoma tumour characteristics.[15,16] To the best of our knowledge, no studies have been performed with national registry data, which limit the effect of selection bias, to demonstrate the impact of delayed COVID-19 diagnostics on melanoma and cSCC tumour characteristics. The aim of this study was therefore to identify the impact of delayed diagnostics due to the COVID-19 pandemic on primary invasive melanoma and cSCC patient and tumour characteristics in the Netherlands.

## Patients and methods

### Study design and data source

In this population-based cohort study, all histopathology reports on all primary cutaneous melanomas and cSCCs between 1 January 2018 and 22 July 2021 were obtained from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA Foundation). This included both first primary melanomas and cSCCs, as well as subsequent melanomas and cSCCs.

### Patient population

Histopathology reports of patients with a primary cutaneous melanoma or cSCC between 2019 and 2021 were included for the final analysis. Primary melanoma histopathology reports were identified by searching for reports registered under relevant retrieval terms (Appendix S1; see Supporting Information). Extracted reports for both primary melanoma and cSCCs included age, sex, and free text of the pathologists' conclusions.

### Data editing and cleaning

Manual review was performed on a selection of pathology reports with a higher likelihood to be incorrectly classified as

new tumour (further described in Appendix S2; see Supporting Information).[17] For melanoma, Breslow thickness was automatically extracted from individual histopathology reports based on the free text using a rule-based algorithm in SAS (SAS Institute Inc., Cary, NC, USA). The algorithm detection of Breslow thickness in melanoma histopathology reports was improved by manually reviewing reports in which no Breslow thickness could be identified. For cSCC, it was not possible to apply a rule-based algorithm to extract tumour diameter and invasion depth from the free text as it was not routinely reported. Therefore, we restricted the analyses to pathology reports from pathology laboratories that used the PALGA protocol for synoptic reporting (51·7%). Diameter, invasion depth, differentiation and high-risk features were registered as separate variables in those reports. Breslow thickness for melanoma, and invasion depth and high-risk features for cases of cSCC were categorized according to the pT 1–4 stages reported in the 8th edition of the American Joint Committee on Cancer melanoma and cSCC tumour–nodes–metastasis staging systems.[18] For both melanoma and cSCC, categorization into substages (e.g. pT4a/b) could not be performed due to the inability to reliably extract relevant histopathological features (e.g. ulceration status for melanoma) from all histopathology reports.

### Time period definitions

Cases of melanoma and cSCC were stratified by year and week number and were further subdivided into: (i) prepandemic (1 January 2019 to 11 March 2020); (ii) first lockdown (12 March 2020 to 31 May 2020); (iii) between first and second lockdowns (1 June 2020 to 13 October 2020); (iv) second lockdown (14 October 2020 to 27 April 2021); and (v) after second lockdown (28 April 2021 to 22 July 2021).

### Statistical analysis

The mean age of patients and Breslow thickness across time periods were compared using an independent t-test. Tumour body locations, pT stage groups and cSCC tumour diameter groups were compared using $\chi^2$-tests. Unknown values of pT stage, body location and Breslow thickness were excluded from statistical comparisons. A subgroup analysis was performed to assess whether the Breslow thickness distribution varied within patients with thick (pT4) melanoma across time periods using the Mann–Whitney U-test. P-values were corrected for multiple comparisons by applying the false discovery rate on all P-values per tumour type and variable.[19]

## Results

### Melanoma

Primary invasive melanoma diagnoses during the pre-COVID (i) and subsequent COVID time periods (ii–v) are presented in Figure 1. A reduction in the incidence of melanoma

diagnoses was observed during the first lockdown, after which a recovery was seen after the lockdown was lifted. No notable reductions in melanoma diagnoses were observed during the second lockdown, but an increase in melanoma diagnoses was seen after the second lockdown. As a result, the cumulative number of primary melanoma diagnoses in 2020 (n = 7720) was lower than in 2019 (n = 7866) (Figure S1; see Supporting Information), but the number of melanomas diagnosed after the second lockdown in 2021 (n = 2439) was higher than in the same period in 2019 (n = 2090).

Stratification of patient and tumour characteristics of primary invasive melanomas registries before and during the COVID pandemic are presented in Table 1. Patients diagnosed with melanoma were slightly younger (mean age 61·5 years, SD 16; P = 0·013) during the first lockdown than the pre-COVID period (mean age 62·8 years, SD 15) and were slightly older during the second lockdown (mean age 64·2 years, SD 15; P ≤ 0·001) and during the period after the second lockdown (mean age 63·5 years, SD 15; P = 0·036). In both post-lockdown periods, the topography distribution of melanoma was less often in the head and neck region (14·5% vs. 15·0%, P = 0·001; 12·8% vs. 15·0%, P < 0·001) and more often on the lower extremities (23·2% vs. 20·1%, P = 0·001; 24·9% vs. 20·1%, P < 0·001) compared with the pre-COVID era.

The mean Breslow thickness did not statistically differ between the pre-COVID era (i) vs. the following time periods (ii–v). In line with this result, stratification of the mean and median Breslow thickness by week number revealed very little variation in thickness during 2019–2021 (Figures S2–S5; see Supporting Information). However, a small shift towards unfavourable pT stages was found during the first lockdown (ii) compared with the pre-COVID time period (i): pT1 52·3% vs. 58·6%; pT2 18·9% vs. 17·8%; pT3 13·2% vs. 11·0%; pT4 9·1% vs. 7·3% (P = 0·001). No relevant changes in pT stage distribution were seen in subsequent periods after the

lockdown. Subgroup analysis of cases of pT4 melanoma revealed a difference in the distribution of Breslow thickness (median 6·2 mm vs. 6·0 mm) diagnosed after the second lockdown (time period v) compared with the pre-COVID timeframe (time period i) (P = 0·011), but other periods showed a distribution comparable with the pre-COVID timeframe.

### Cutaneous squamous cell carcinoma

As presented in Figure 2, a steep decline in the incidence of cSCC diagnoses was seen during the first, but not during the second lockdown. In contrast to melanoma incidence, no notable surge in cSCC diagnoses was observed after the second lockdown. During week 29 of 2021, which was the most recent included week in this study, the cumulative number of cSCC registries (n = 15 153) was higher than in the same week in 2019 (n = 14 191) and 2020 (n = 13 489) (Figure S6; see Supporting Information).

There was no clinically meaningful difference (i.e. < 4 months) in the age distribution of patients with cSCC between the pre-COVID timeframe (i) and the subsequent timeframes (ii-v) (Table 2). With regard to topography distribution, the post-lockdown periods (iii and v), which were both in the spring and summer season, showed slightly fewer tumours in the head and neck area (by about 4%) and more tumours on the upper extremities (by about 2%) compared with the pre-COVID timeframe (Table 2). The mean invasion depth of SCCs was slightly lower during the timeframe between the first and second lockdowns (3·0 vs. 3·1, P = 0·013), during the second lockdown (3·0 vs. 3·1, P < 0·001) and after the second lockdown (2·9 vs. 3·1, P < 0·001) compared with the pre-COVID timeframe. Stratification of the mean and median invasion depth on week number reveals an almost homogeneous distribution during 2019–2021 (Figures S7–S10; see Supporting Information). Furthermore, comparison of the
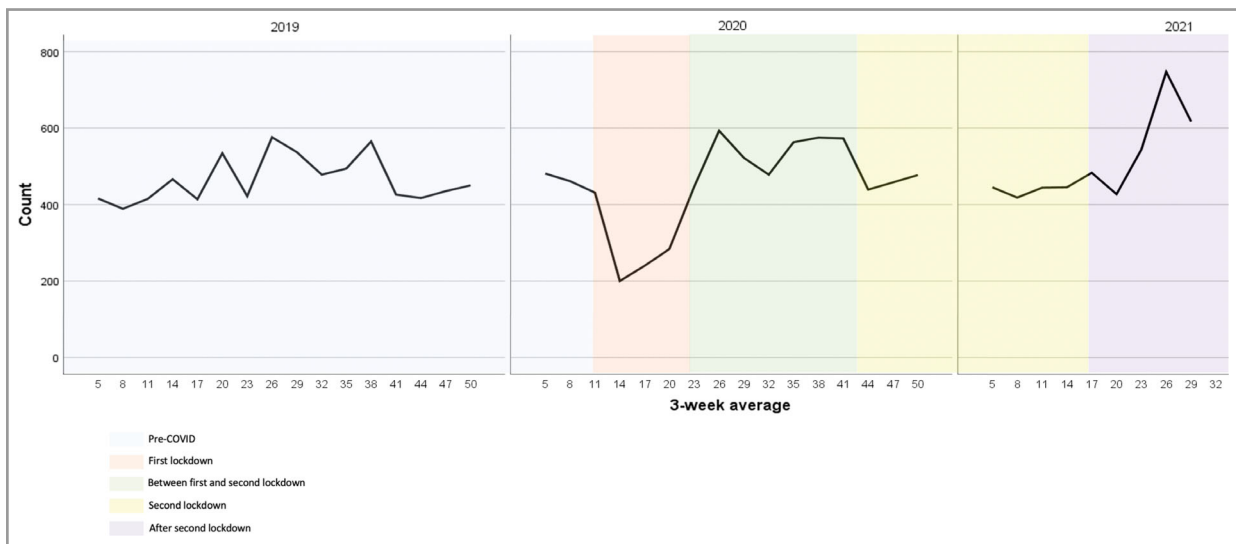


**Figure 1** Cases of primary melanoma in the Netherlands during 2019–2021.

**Table 1** Baseline and tumour characteristics of invasive melanomas diagnosed before and during the COVID-19 pandemic in the Netherlands

| | Time period i | Time period ii | P-value[a] | Time period iii | P-value[a] | Time period iv | P-value[a] | Time period v | P-value[a] |
|---|---|---|---|---|---|---|---|---|---|
| Total number | 9377 | 1037 | | 3532 | | 4049 | | 2439 | |
| Age (years) | | | | | | | | | |
| Mean (SD) | 62·8 (15) | 61·5 (16) | 0·013* | 63·1 (15) | 0·32 | 64·2 (15) | < 0·001* | 63·5 (15) | 0·036* |
| Median (IQR) | 64 (53–74) | 62 (50–73) | | 64 (53–75) | | 66 (54–76) | | 65 (53–75) | |
| Sex, n (%) | | | | | | | | | |
| Male | 4704 (50·2) | 495 (47·7) | | 1727 (48·9) | | 2049 (50·6) | | 1131 (46·4) | |
| Female | 4673 (49·8) | 542 (52·3) | | 1805 (51·1) | | 2000 (49·4) | | 1308 (53·6) | |
| Topography, n (%) | | | | | | | | | |
| Head and neck | 1406 (15·0) | 154 (14·9) | 0·52 | 512 (14·5) | 0·001* | 640 (15·8) | 0·059 | 311 (12·8) | < 0·001* |
| Trunk | 3281 (35·0) | 347 (33·5) | | 1156 (32·7) | | 1465 (36·2) | | 763 (31·3) | |
| Upper extremity | 1907 (20·3) | 230 (22·2) | | 704 (19·9) | | 780 (19·3) | | 556 (22·8) | |
| Lower extremity | 1884 (20·1) | 215 (20·7) | | 820 (23·2) | | 750 (18·5) | | 606 (24·9) | |
| Unknown | 899 (9·6) | 91 (8·8) | | 340 (9·6) | | 414 (10·2) | | 203 (8·3) | |
| Tumour thickness (mm) | | | | | | | | | |
| Mean (SE) | 1·50 (0·02) | 1·66 (0·067) | 0·034 | 1·48 (0·03) | 0·46 | 1·51 (0·036) | 0·97 | 1·59 (0·052) | 0·15 |
| Median (IQR) | 0·80 (0·50–1·60) | 0·90 (0·50–1·90) | | 0·80 (0·50–1·60) | | 0·70 (0·50–1·60) | | 0·80 (0·50–1·50) | |
| pT1 (≤ 1·00) | 5497 (58·6) | 542 (52·3) | 0·001* | 2052 (58·1) | 0·56 | 2387 (59·0) | 0·10 | 1420 (58·2) | 0·045 |
| pT2 (1·01–2·00) | 1668 (17·8) | 196 (18·9) | | 634 (18·0) | | 646 (16·0) | | 455 (18·7) | |
| pT3 (2·01–4·00) | 1029 (11·0) | 137 (13·2) | | 404 (11·4) | | 417 (10·3) | | 224 (9·2) | |
| pT4 (> 4·00) | 681 (7·3) | 94 (9·1) | | 234 (6·6) | | 307 (7·6) | | 195 (8·0) | |
| Unknown | 502 (5·4) | 68 (6·6) | | 208 (5·9) | | 292 (7·2) | | 145 (5·9) | |

IQR, interquartile range. Time periods: (i) pre-COVID (1 January 2019 to 11 March 2020); (ii) first lockdown (12 March 2020 to 11 March 2020); (iii) between first and second lockdowns (1 June to 13 October 2020); (iv) second lockdown (14 October 2020 to 27 April 2021); (v) after second lockdown (28 April 2021 to 22 July 2021); (v) between first and second lockdowns (1 June to 13 October 2020). [a]Baseline and tumour characteristics were compared with pre-COVID data using an independent t-test for continuous variables and a $\chi^2$-test for categorical variables. *Significant result after false discovery rate correction was applied.
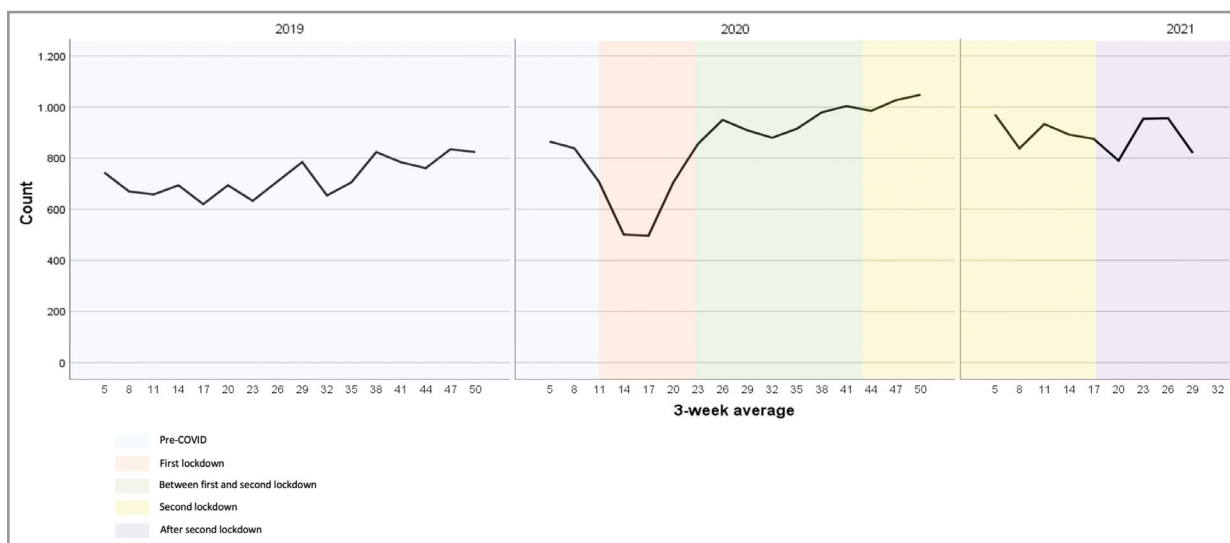
**Figure 2** Cases of primary cutaneous squamous cell carcinoma in the Netherlands during 2019–2021.

cSCCs pT stage distribution revealed no significant change between the pre-COVID (i) and subsequent COVID timeframes (ii–v).

## Discussion

This nationwide study of a delayed diagnosis of melanoma and cSCC revealed only a minor shift towards unfavourable melanoma pT stages during the first lockdown in the Netherlands and no impact on the time periods afterwards. This is a remarkable finding because a priori an unfavourable effect of a delayed diagnosis was expected.[2,10]

One explanation for our findings could be that although a rebound in melanoma and cSCC diagnoses was observed after the first lockdown, not all undiagnosed melanomas and cSCCs are yet diagnosed in the period of this study. However, given the long follow-up time of >1 year after the first lockdown it seems unlikely that many aggressive skin tumours are still undetected. Furthermore, the limited impact on tumour characteristics may be explained by a slower than previously assumed growth rate of melanomas and cSCCs. Studies reporting on the tumour growth rates of these skin cancer types are typically based on patients' recalled dates of first noticing a skin lesion, the first moment of considering this lesion suspicious, and the date of diagnosis or excision.[20–23] However, the varying reliability of patients to accurately recall these dates may limit the reliability of these studies. Nevertheless, prediction models estimating an unfavourable effect on tumour diameter and prognosis due to delayed diagnostics were based on these studies.[2,10]

Our study revealed an increased Breslow thickness for cases of pT4 melanoma in the last time period (v) compared with the pre-COVID timeframe, suggesting that thick melanomas have grown slightly thicker due to delayed diagnostics. However, this effect was only observed during the last timeframe,

and would have been observable in an earlier time period after the first lockdown if melanomas were indeed growing as fast as previously reported. This finding strengthens the hypothesis that melanomas and cSCCs may grow slower than previously assumed. A third hypothesis could be that only slow-growing tumours were delayed in being diagnosed and that the diagnosis of fast-growing tumours, despite the pandemic, was not delayed.

Although a limited impact on tumour characteristics was found in this study, the impact of the pandemic on skin cancer treatment should not be dismissed. A recent study reported a significant delay in immunotherapy treatment of patients with advanced melanoma in the Netherlands. Moreover, a significant increase in brain metastases and worse performance status was found during the second lockdown.[24] While the increase in brain metastases may have resulted from improved screening instead of treatment delay, these results still suggest an unfavourable impact on patients with advanced melanoma care during the pandemic.

A strength of this study is the use of nationwide registry data, thereby including all histopathology confirmed invasive melanomas and cSCCs in the Netherlands, which avoided the occurrence of selection bias. Another strength is the use of an algorithm to extract tumour characteristics, allowing for faster reporting of the impact of delayed diagnostics during the pandemic compared with manual registration of patient data. Nevertheless, our study was limited by focusing on a small number of high-risk primary tumour characteristics of melanoma and cSCC and did not take into account the distribution of patients with lymph node or distant metastasis across the different time periods.

In conclusion, this study revealed a limited impact of delayed diagnostics due to the COVID-19 pandemic on cSCC and melanoma tumour characteristics in the Netherlands. Follow-up studies in the coming years are needed to identify

**Table 2** Baseline and tumour characteristics of cutaneous squamous cell carcinomas (cSCCs) diagnosed before and during the COVID-19 pandemic in the Netherlands

| | Time period i | Time period ii | P-value[a] | Time period iii | P-value[a] | Time period iv | P-value[a] | Time period v | P-value[a] |
|---|---|---|---|---|---|---|---|---|---|
| Total number | 31 654 | 4175 | | 11 541 | | 14 930 | | 6532 | |
| Age (years) | | | | | | | | | |
| Mean (SD) | 76·8 (10·5) | 76·4 (10·2) | 0·070 | 77·2 (10·2) | < 0·001* | 77·2 (10·3) | < 0·001* | 77·2 (10·0) | 0·002* |
| Median (IQR) | 78 (71–84) | 77 (71–84) | | 78 (72–84) | | 78 (72–84) | | 78 (72–84) | |
| Sex, n (%) | | | | | | | | | |
| Male | 18 216 (57·5) | 2446 (58·6) | | 6504 (56·4) | | 8688 (58·2) | | 3709 (56·8) | |
| Female | 13 438 (42·5) | 1729 (41·4) | | 5037 (43·6) | | 6242 (41·8) | | 2823 (43·2) | |
| Topography, n (%) | | | | | | | | | |
| Head and neck | 17 757 (56·1) | 2275 (54·5) | 0·018* | 6006 (52·0) | < 0·001* | 8453 (56·6) | 0·28 | 3435 (52·6) | < 0·001* |
| Trunk | 1910 (6·0) | 287 (6·9) | | 765 (6·6) | | 962 (6·4) | | 442 (6·8) | |
| Upper extremity | 4731 (14·9) | 650 (15·6) | | 2013 (17·4) | | 2239 (15·0) | | 1093 (16·7) | |
| Lower extremity | 3246 (10·3) | 470 (11·3) | | 1292 (11·2) | | 1482 (9·9) | | 725 (11·1) | |
| Unknown | 4010 (12·7) | 493 (11·8) | | 1465 (12·7) | | 1794 (12·0) | | 837 (12·8) | |
| cSCCs registered with synoptic reporting, n (%) | 15 084 (47·7) | 2301 (55·1) | | 6013 (52·1) | | 8474 (56·8) | | 3718 (56·9) | |
| Invasion depth (mm), n (%) | | | | | | | | | |
| Mean (SD) | 3·09 (2·05) | 3·19 (2·03) | 0·057 | 3·01 (1·97) | 0·013* | 2·98 (1·93) | < 0·001* | 2·88 (1·84) | < 0·001* |
| Median (IQR) | 2·7 (1·8–4·0) | 2·8 (1·9–4·0) | | 2·5 (1·8–4·0) | | 2·5 (1·8–3·9) | | 2·5 (1·7–3·7) | |
| pT1 (≤ 1·00) | 11 174 (74·1) | 1689 (73·4) | 0·25 | 4391 (73·0) | 0·74 | 6270 (74·0) | 0·080 | 2729 (73·4) | 0·036 |
| pT2 (1·01–2·00) | 840 (5·6) | 131 (5·7) | | 337 (5·6) | | 528 (6·2) | | 231 (6·2) | |
| pT3 (2·01–4·00) | 1105 (7·3) | 197 (8·6) | | 417 (6·9) | | 575 (6·8) | | 226 (6·1) | |
| pT4 (> 4·00) | 6 (0·0) | 1 (0·0) | | 1 (0·0) | | 5 (0·1) | | 1 (0·0) | |
| Unknown | 1959 (13·0) | 283 (12·3) | | 867 (14·4) | | 1096 (12·9) | | 531 (14·3) | |

IQR, interquartile range. Time periods: (i) pre-COVID (1 January 2019 to 11 March 2020); (ii) first lockdown (12 March 2020 to 31 May 2020); (iii) between first and second lockdowns (1 June to 13 October 2020); (iv) second lockdown (14 October 2020 to 27 April 2021); (v) after second lockdown (28 April 2021 to 22 July 2021). [a]Baseline and tumour characteristics were compared with pre-COVID data using an independent t-test for continuous variables and a $\chi^2$-test for categorical variables. *Significant result after false discovery rate correction was applied.

the impact on patients' survival due to postponed treatments or still undiagnosed skin cancer cases.

## Acknowledgments

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Appendix S1** Collection of melanoma pathology reports.

**Appendix S2** Manual review of pathology reports.

**Figure S1** Cumulative number primary invasive melanoma diagnoses registered during 2019–2021, stratified by week number.

**Figure S2** Mean Breslow thickness of primary melanomas registered during 2019–2021, stratified by week number.

**Figure S3** Median Breslow thickness of primary melanomas registered during 2019–2021, stratified by week number.

**Figure S4** Melanoma Breslow thickness box plots for 2019–2021, stratified by week number.

**Figure S5** Melanoma Breslow thickness scatter plots for 2019–2021, stratified by week number.

**Figure S6** Cumulative number of primary cutaneous squamous cell carcinoma diagnoses registered during 2019–2021, stratified by week number.

**Figure S7** Mean invasion depth of primary cutaneous squamous cell carcinomas registered during 2019–2021, stratified by week number.

**Figure S8** Median invasion depth of primary cutaneous squamous cell carcinomas registered during 2019–2021, stratified by week number.

**Figure S9** Cutaneous squamous cell carcinoma invasion depth box plots for 2019–2021, stratified by week number.

**Figure S10** Cutaneous squamous cell carcinoma invasion depth scatter plots for 2019–2021, stratified by week number.