



# Melanoma care during one year pandemic in Berlin: decreasing appointment cancellations despite increasing COVID-19 concern

Aleksandra Micek<sup>1,2</sup>, Katharina Diehl<sup>3,4</sup>, Miriam Teuscher<sup>5</sup>, Marthe-Lisa Schaarschmidt<sup>6</sup>, Bianca Sasama<sup>5</sup>, Jan Ohletz<sup>1</sup>, Guido Burbach<sup>1</sup>, Felix Kiecker<sup>7</sup>, Uwe Hillen<sup>7</sup>, Wolfgang Harth<sup>1</sup>, Wiebke K. Peitsch<sup>5</sup>

(1) Department of Dermatology and Allergology, Vivantes Klinikum Spandau, Berlin, Germany

(2) Faculty of Medicine, Charité University Medicine Berlin, Berlin, Germany

(3) Mannheim Institute of Public Health, Social and Preventive Medicine, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

(4) Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany

(5) Department of Dermatology and Phlebology, Vivantes Klinikum im Friedrichshain, Berlin, Germany

(6) Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, Heidelberg University, Mannheim, Germany

(7) Department of Dermatology and Venereology, Vivantes Klinikum Neukölln, Berlin, Germany

## Summary

**Background and objectives:** The COVID-19 pandemic poses a great challenge for cancer patients. Our aim was to assess its influence on treatment and appointments of melanoma patients after one year of pandemic.

**Methods:** Melanoma patients treated in the Vivantes Skin Cancer Centre in Berlin, Germany completed a postal survey on pandemic-related alterations in melanoma care. Impact factors on changes of appointments were examined with descriptive analyses and multivariate logistic regression. Data after one year of pandemic were compared to those after its first wave.

**Results:** Among 366 participants (57.7 % males; mean age 69.2 years, response rate: 36.1 %), 38 (10.1 %) reported postponed or missed appointments, mostly on their own demand (71.1 %) due to fear of COVID-19 (52.6 %). Current treatment was associated with a lower risk of changing appointments (Odds Ratio [OR]: 0.194,  $p = 0.002$ ), higher age (OR: 1.037,  $p = 0.039$ ), longer disease duration (OR: 1.007,  $p = 0.028$ ), and higher school degree (OR: 2.263,  $p = 0.043$ ) with higher probability. Among 177 patients currently receiving therapy, only 1.7 % experienced pandemic-related treatment alterations. Concern about COVID-19 was significantly higher after one year of pandemic than after its first wave, but the number of missed appointments was lower.

**Conclusions:** Pandemic-related changes were rare in our cohort and decreased over time despite increasing concern.

## Introduction

The COVID-19 pandemic led to an international emergency affecting health care systems globally. As of 30 Jul 2021, > 196 million cases were confirmed worldwide [1], including 3,766,765 in Germany and 182,557 in Berlin

[2]. To ensure sufficient capacities for patients with COVID-19, medical facilities were rapidly reorganized [3]. Resources were rededicated, resulting in cancellations or suspensions of regular health care procedures [4]. Broad precaution strategies and safety measures were implemented [5].

Oncological patients, including those with skin cancer, are particularly threatened by the pandemic [3, 6]. In many countries, the unprecedented overwhelm of health care facilities with COVID-19 patients required postponements of their consultations and elective surgeries. Furthermore, cancer patients are considered particularly vulnerable because of their immunosuppressed status [7] and are presumed to have higher risk of contracting infections [8] and suffer from severe COVID-19 courses [9, 10].

Delays in diagnosis, surgery, systemic therapy and follow-ups due to the pandemic are related to more advanced tumor stage, poorer outcome and increased mortality [6, 11, 12]. According to an Australian study, the monthly referral numbers of primary melanoma cases decreased by 48.0 % during the first lockdown in March 2020 compared to the same periods in 2017–2019 [12]. Significant reductions of melanoma diagnoses and/or follow-up visits were also reported from Italy [13–16], England [17], Germany [18], Canada [19] and the USA [20], highlighting the severity and global scale of the problem.

Shortly after the first wave of the pandemic, we conducted a postal survey (Mela-COVID) to assess alterations of treatments and appointments of melanoma patients from the Vivantes Skin Cancer Center located in three districts in Berlin, Germany (Figure 1) [21]. The aim of the *Mela-COVID Follow-up study* presented here was to investigate the impact of COVID-19 on melanoma-related treatment and appointments after one year of pandemic and to identify reasons and determinants for alterations.

## Patients and methods

### Study population

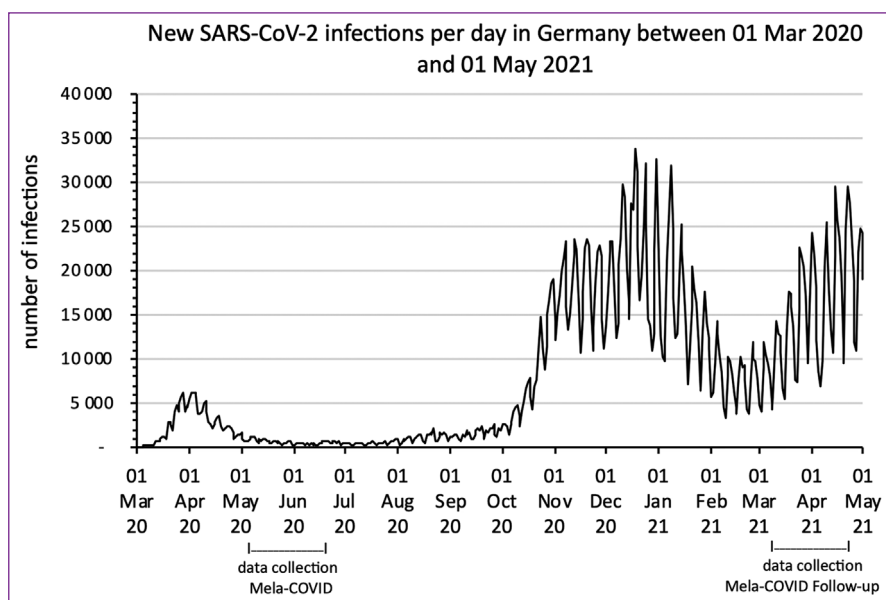
Patients with melanoma who received treatment and/or consultations and/or examinations in the Vivantes Skin Cancer Center between 01 Jan 2019 and 01 Mar 2021 were candidates for participation. Eligible patients were identified through case lists prepared for certification as cancer center. Inclusion criteria were diagnosis of melanoma stage I–IV according to the 8<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) staging system, age  $\geq$  18 years and ability to provide informed consent.

The study was performed accordant to the principles of the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Medicine of Charité University Medicine Berlin (amendment to EA4/082/20).

### Data collection

Data were collected between 01 Mar 2021 and 30 Apr 2021. A patient information, two copies of an informed consent form and a study questionnaire were sent to all study candidates by post. Patients willing to participate were asked to return one copy of the signed informed consent and the completed questionnaire in a prepaid envelope.

The survey contained questions about sociodemographic data (age, sex, marital status, household members, education, employment), disease duration, treatment since March



**Figure 1** Number of new SARS-CoV-2 infections per day between 01 Mar 2020 and 01 May 2021 in Germany. Source: Robert Koch-Institute, available at: [https://www.rki.de/DE/Content/InfAZ/N/Neuartiges\\_Coronavirus/Daten/Fallzahlen\\_Kum\\_Tab.html?fbclid=IwARoddnAvxHA-nN5EIOfQfE-DUjFiH7rmeDeS1tYTlsvQ6Bo4FT-Scso8S5dpA](https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Daten/Fallzahlen_Kum_Tab.html?fbclid=IwARoddnAvxHA-nN5EIOfQfE-DUjFiH7rmeDeS1tYTlsvQ6Bo4FT-Scso8S5dpA) (accessed 28 Jun 2021). Bars: Data collection periods of the Mela-COVID and the Mela-COVID Follow-up study.

2020 and treatment experience. Comorbid diseases including arterial hypertension, cardiovascular, pulmonary, immunological, liver, metabolic, thyroid, renal and mental diseases, non-melanoma skin cancer and other malignancies could be chosen from a list. Other comorbid diseases could be specified as free text. Moreover, participants were asked about SARS-CoV-2 infections affecting themselves, household members and/or close acquaintances and about the treatment setting (outpatient, inpatient or intensive care unit [ICU]). Concern about COVID-19 and melanoma was assessed on 5-point scales (1 = none, 5 = very much) and on scales from 0 (no concern) to 100 (highest concern).

Further questions referred to alterations in melanoma-related treatment (postponement, pause, stop or change) and/or appointments (postponement or cancellation) due to the pandemic. Participants reporting alterations were asked to specify whether the change emerged on their own request or was determined by the medical provider. Reasons for alterations could be chosen from a list (fear of SARS-CoV-2 infection, sickness, risk-benefit consideration, lack of resources, closed doctor's office or other reasons) or described as free text. Additionally, patients had to indicate participation in the Mela-COVID study in May–Jun 2020 (yes/no) [21].

Patients' medical history comprising information on the melanoma disease (time since diagnosis, AJCC 2017 stage, tumor manifestations), treatment since 01 Mar 2020 (kind, goal [adjuvant/palliative], response), changes of treatment and/or appointments, treatment experience and comorbidities were extracted from medical records by AM and reconciled with the patients' answers. Reported impact of the pandemic was categorized into patient- and medical provider-related. In case of missing or inconsistent data, participants were contacted by phone or post to receive clarifying information.

## Statistical analyses

For subgroup analyses, participants were stratified based on sociodemographic characteristics like age, sex, marital status (single or widowed vs. married or in a partnership), school degree (low or intermediate vs. high, A-levels, "Abitur" or "Fachabitur"), employment (yes/no), melanoma-related characteristics (disease duration, AJCC 2017 stage, I vs. II vs. III vs. IV), tumor burden (yes/no) and treatment since 01 Mar 2020 (yes/no. If treatment, kind (surgery, radiotherapy, systemic treatment), treatment experience, comorbidities (yes/no; < 5 vs.  $\geq$  5), concern about COVID-19 and melanoma (none vs. little vs. some vs. much vs. very much; scale 0–100), and SARS-CoV-2 infections affecting participants (yes/no), their household members (yes/no) or close acquaintances (yes/no). Differences between groups were tested for statistical

significance using Chi-square tests or Fisher's exact test for categorical variables and Mann-Whitney-U tests for linear variables due to lack of normal distribution.

Associations between characteristics and appointment changes were further examined using multiple logistic regression analysis. The basic model contained postponed/misused appointments as dependent variable and sex, age, AJCC stage, current treatment (since 01 Mar 2020, yes/no), number of comorbidities (< 5 vs.  $\geq$  5), concern about COVID-19 and melanoma (both on 0–100 scales), disease duration and school degree (low/intermediate vs. high) as independent variables. Differences were considered significant with a p-value of < 0.05.

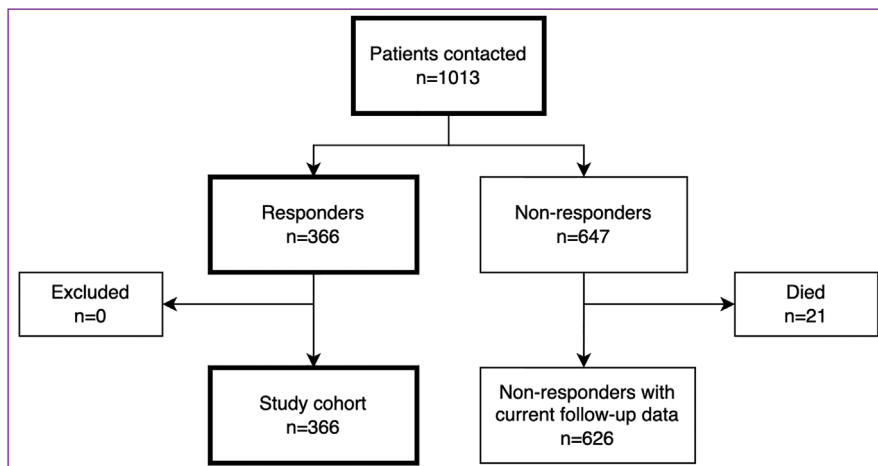
The subcohort participating both in the Mela-COVID and the Mela-COVID Follow-up study was investigated further in additional analyses. In participants of this subcohort reporting changes in treatments and/or appointments, the time of alteration (during the first wave, thereafter, or both) was documented. Furthermore, concern about COVID-19 and melanoma, concern to continue treatment, social and professional contact reduction reported in the Mela-COVID and the Mela-COVID Follow-up survey were compared and tested for statistical significance with Chi-square tests or Mann-Whitney-U tests.

## Results

Participation was offered to 1,013 patients; 366 gave written informed consent and completed the questionnaire (response rate: 36.1 %; recruitment process flowchart: Figure 2). Data from all questionnaires were included into the final analysis. Compared to living non-responders (n = 626), the group of responders contained a higher proportion of males (p = 0.012), had a higher mean age (p = 0.023) and obtained treatment of their melanoma during the pandemic (p = 0.010), particularly systemic medication (p = 0.002), more frequently (online supplementary Table S1).

### Characteristics of the study cohort

57.7 % of the participants were male, and the mean age was 69.2 years (Table 1). The majority lived in a partnership (71.9 %). 51.0 % had a high school degree, and 25.7 % were working. Half had melanoma stage I, 18.0 % stage II, 16.9 % stage III and 15.0 % stage IV. The mean disease duration was 39.1 months. Tumor burden was present in 39.3 % during the pandemic and in 10.1 % at the time of study participation (Table 1). 48.8 % of the participants received treatment between 01 Mar 2020 and data collection, most frequently surgery (34.4 %), followed by systemic therapy (21.6 %) and radiotherapy (3.6 %; Table 2). The treatment intention was curative in 70.6 %.



**Figure 2** Recruitment process flowchart of the Mela-COVID Follow-up study.

One-third (33.1 %) suffered from  $\geq 5$  comorbidities. Details on comorbidities in the whole cohort and in subgroups with and without cancelled appointments are shown in online supplementary Table S2.

### Impact of the COVID-19 pandemic

Six patients (1.6 %) experienced SARS-CoV-2 infections; one of these was treated inpatient on an isolation ward and one on an ICU (Table 3). None of the infections was acquired during a melanoma-related appointment or hospital stay. 1.9 % reported SARS-CoV-2 infections among household members and 31.4 % among close acquaintances.

Mean concern about COVID-19 was 45.1 on a 0–100 scale, mean concern about melanoma 40.4. The majority of the respondents reduced their social contacts very much (55.2 %) or much (29.0 %) due to the pandemic. Professional contacts were decreased very much by 34.0 % and much by 14.0 % of working participants. The vast majority (89.6 %) were willing to be vaccinated against COVID-19. 34.1 % were interested in telemedicine, most frequently, in consultations by phone (78.4 %), followed by video consultations (28.8 %) and apps (21.6 %).

### Changes in treatment

Out of 177 patients receiving therapy, three (1.7 %) experienced treatment alterations due to the pandemic, two during the first wave and one thereafter. In the first, postoperative radiotherapy of an intracerebral metastasis was changed to a hypofractionated schedule. In the second, re-excision of the primary melanoma with safety margins and sentinel lymph node biopsy (SLNB) were postponed on the patient's demand. In the third, primary melanoma excision with 2 cm margins and SLNB were delayed by four weeks due to lack of capacities for anesthesia.

### Changes in appointments

Alterations in melanoma-related appointments due to the pandemic were reported by 38 participants (10.1 %), most frequently on their own request (71.1 %) due to fear of COVID-19 (52.6 %). Fear of acquiring COVID-19 from other patients was stated most commonly (39.5 %), followed by fear of infection during transport (18.4 %) or from medical staff (13.1 %). 28.9 % of the appointment changes were medical provider-related (Figure 3).

Subgroup comparisons according to postponed or missed appointments showed that tumor manifestation ( $p = 0.002$ ) (Table 1) and treatment during the pandemic ( $p < 0.001$ ) (Table 2) as well as no or little concern to continue treatment ( $p = 0.006$ ) (Table 3) were associated with lower proportions of postponed/missed appointments, whereas longer disease duration ( $p = 0.001$ ) and high school degree ( $p = 0.047$ ) were positively associated with appointment changes (Table 1).

Multivariate regressions analysis confirmed significant associations between current treatment (OR: 0.194,  $p = 0.002$ ), increasing disease duration (OR: 1.007,  $p = 0.028$ ) and higher school degree (OR: 2.263,  $p = 0.043$ ) on the one hand and changes in appointments on the other hand (Table 4). Furthermore, the models suggested a higher probability of missing appointments with increasing age (OR: 1.037,  $p = 0.039$ ) and by trend with increasing concern about COVID-19 (OR: 1.581,  $p = 0.060$ ). Other sociodemographic, disease- and treatment-related characteristics and comorbidities showed no significant associations with postponing/missing an appointment (Tables 1, 2, 3, online supplementary Table S3).

### Impact of the pandemic during its first wave and thereafter

216 of 366 participants (59.0 %) participated both in the Mela-COVID study in May–June 2020 and in the present

**Table 1** Patient and disease characteristics of the whole cohort and subgroups that did or did not postpone/miss appointments.

Characteristic	Whole cohort		Postponed/missed appointments		p <sup>c</sup>
	n = 366 <sup>a</sup>		Yes, n = 38 <sup>a</sup>	No, n = 328 <sup>a,b</sup>	
	n (%)	n (%)	n (%)	n (%)	
<b>Sex</b>					
Female	155 (42.3)	14 (36.8)	141 (43.0)		0.468
Male	211 (57.7)	24 (63.2)	187 (57.0)		
<b>Age, years</b>					
Mean (SD)	69.2 (12.9)	72.6 (10.2)	68.6 (13.6)		0.164
Median (IQR, range)	71.0 (18, 25–96)	73.0 (13, 52–91)	70.5 (19, 25–96)		
<b>Partnership</b>					
Single <sup>d</sup>	103 (28.1)	9 (23.7)	94 (28.7)		0.519
Partner <sup>e</sup>	263 (71.9)	29 (76.3)	234 (71.3)		
<b>School degree<sup>f</sup></b>					
Low/intermediate	174 (49.0)	12 (33.3)	162 (50.8)		0.047
High <sup>g</sup>	181 (51.0)	24 (66.7)	157 (49.2)		
<b>Employment</b>					
Not working	272 (74.3)	29 (76.3)	243 (74.1)		0.766
Working	94 (25.7)	9 (23.7)	85 (25.9)		
<b>AJCC 2017 stage</b>					
I	183 (50.0)	18 (47.4)	165 (50.3)		0.697
II	66 (18.0)	9 (23.7)	57 (17.4)		
III	62 (16.9)	7 (18.4)	55 (16.8)		
IV	55 (15.0)	4 (10.5)	51 (15.5)		
<b>Disease duration</b>					
Mean (SD)	39.1 (52.6)	57.4 (71.6)	36.9 (49.6)		0.001
Median (IQR, range)	25.0 (32, 0–482)	35.5 (33.3, 9–398)	24.0 (32.0, 0–482)		
≤ 12 months	89 (24.3)	2 (5.3)	87 (26.5)		0.028
> 1–3 years	159 (43.4)	19 (50.0)	140 (42.7)		
> 3–5 years	69 (18.9)	9 (23.7)	60 (18.3)		
> 5 years	49 (13.4)	8 (21.1)	41 (12.5)		
<b>Tumor burden during pandemic</b>					
No	329 (89.9)	36 (94.7)	293 (89.3)		0.295
Yes	37 (10.1)	2 (5.3)	35 (10.7)		
Primary melanoma	0 (0.0)	0 (0.0)	0 (0.0)		
Regional LN metastases	3 (0.8)	0 (0.0)	3 (0.9)		
<b>Satellite or in-transit metastases</b>					
metastases	3 (0.8)	1 (2.6)	2 (0.6)		
Distant metastases	31 (8.5)	1 (2.6)	30 (9.1)		

Continued

Table 1 Continued.

Characteristic	Whole cohort		Postponed/missed appointments		p <sup>c</sup>
	n = 366 <sup>a</sup>		Yes, n = 38 <sup>a</sup>	No, n = 328 <sup>a,b</sup>	
	n (%)	n (%)	n (%)	n (%)	
Melanoma manifestation during pandemic					
No (remission)	222 (60.7)	32 (84.2)	190 (57.9)		0.002
Yes	144 (39.3)	6 (15.8)	138 (42.1)		
Curative treatment	94 (65.3)	3 (50.0)	91 (65.9)		
Tumor burden	50 (34.7)	3 (50.0)	47 (34.1)		
Comorbidities					
No	21 (5.7)	3 (7.9)	18 (5.5)		0.546
Yes	345 (94.3)	35 (92.1)	310 (94.5)		
< 5	245 (66.9)	26 (68.4)	219 (66.8)		0.838
≥ 5	121 (33.1)	12 (31.6)	109 (33.2)		

<sup>a</sup>The total number of participants in each group was set to 100 %.

<sup>b</sup>The subgroup of participants who did not postpone or miss appointments included n = 7 patients who did not have any melanoma-related appointments scheduled during the pandemic.

<sup>c</sup>Differences between the subgroups that did or did not postpone/miss appointments were tested for significance with Chi-square test for binary and categorical variables and with Mann-Whitney-U test for linear variables.

<sup>d</sup>Single, divorced or widowed.

<sup>e</sup>In a partnership or married.

<sup>f</sup>Missing data: school degree n = 11.

<sup>g</sup>A-levels ("Abitur" or "Fachabitur").

Abbr.: AJCC, American Joint Committee on Cancer; IQR, interquartile range; LN, lymph node; n, number; SD, standard deviation. Significant findings are highlighted in italic.

study. A recruitment process flowchart of both studies is shown as online supplementary Figure S1. Sociodemographic, disease and treatment characteristics of participants in both studies are presented in online supplementary Tables S3 and S4.

Compared to May-June 2020, i.e. shortly after the first wave of the pandemic in Germany, concern about COVID-19 was significantly higher after one year of pandemic (35.3 vs. 42.9 on a 0–100 scale,  $p < 0.001$ ) (Table 5, Figure 4). Furthermore, patients were more likely to reduce social contacts ( $p = 0.001$ ) (Table 5). However, the number of patients who postponed/missed appointments was higher during the first wave ( $n = 29$ , 13.4 %; 95 % confidence interval [CI]: 9.0–18.2) than in the nine months thereafter ( $n = 19$ , 8.8 %, 95 % CI = 5.1–12.9) (Table 5). Current treatment was the main factor associated with a higher likelihood of keeping appointments ( $p = 0.005$ ) (online supplementary Table S4).

## Discussion

Delay in skin cancer screening and follow-up due to the pandemic was shown to result in a higher incidence of advan-

ced skin cancers and an increased thickness of melanomas after COVID-19-induced lockdowns, with the consequence of a poorer prognosis [11, 14]. In a growth rate model, melanoma-related 10-year survival was predicted to decrease by 2.4 % after a 3-month diagnostic delay [22]. These findings emphasize the importance of maintaining regular treatment schedules and follow-up visits for skin cancer patients despite the pandemic. Our study revealed only few treatment changes and a relatively low rate of postponed or missed appointments during one year of pandemic.

## Changes in treatment

Only three participants underwent treatment changes related to the pandemic. Radiotherapy was switched to a hypofractionated schedule following recommendations by radiotherapist associations [23]. Surgery was postponed in one case on the patient's request and in the other regrettably due to limited anesthesiological resources.

According to consensus guidelines for the management of melanoma during the COVID-19 pandemic, care of cancer

**Table 2** Treatment characteristics of the whole cohort and subgroups that did or did not postpone/miss appointments.

Characteristic	Whole cohort		Postponed/missed appointments		p <sup>c</sup>		
	n = 366 <sup>a</sup>		Yes, n = 38 <sup>a</sup>			No, n = 328 <sup>a,b</sup>	
	n (%)	n (%)	n (%)	n (%)		n (%)	
Treatment during pandemic <sup>d</sup>							
No	189 (51.6)	31 (81.6)	158 (48.2)	< 0.001			
Yes	177 (48.4)	7 (18.4)	170 (51.8)				
Kind of treatment <sup>e</sup>							
Surgery							
No	240 (65.6)	33 (86.8)	207 (63.1)	0.004			
Yes	126 (34.4)	5 (13.2)	121 (36.9)				
Primary melanoma surgery <sup>f</sup>							
No	263 (72.1)	35 (92.1)	228 (69.7)	0.004			
Yes	102 (27.9)	3 (7.9)	99 (30.3)				
SLNB							
No	321 (87.7)	37 (97.4)	284 (86.6)	0.055			
Yes	45 (12.3)	1 (2.6)	44 (13.4)				
CLND							
No	363 (99.2)	38 (100.0)	325 (99.1)	0.554			
Yes	3 (0.8)	0 (0.0)	3 (0.9)				
Surgery of other metastases							
No	341 (93.2)	36 (94.7)	305 (93.0)	0.686			
Yes	25 (6.8)	2 (5.3)	23 (7.0)				
Radiotherapy							
No	353 (96.4)	37 (97.4)	316 (96.3)	0.746			
Yes	13 (3.6)	1 (2.6)	12 (3.7)				
Systemic treatment <sup>g</sup>							
No	286 (78.4)	35 (92.1)	251 (76.8)	0.030			
Yes	79 (21.6)	3 (7.9)	76 (23.2)				
ICI <sup>g</sup>							
No	298 (81.4)	36 (94.7)	262 (79.9)	0.026			
Yes	68 (18.6)	2 (5.3)	66 (20.1)				
BRAF/MEK inhibitors <sup>h</sup>							
No	350 (95.6)	36 (94.7)	314 (95.7)	0.776			
Yes	16 (4.4)	2 (5.3)	14 (4.3)				
Chemotherapy							
No	363 (99.5)	38 (100.0)	325 (99.4)	0.629			
Yes	2 (0.5)	0 (0.0)	2 (0.6)				

Continued



Table 2 Continued.

Characteristic	Whole cohort		Postponed/missed appointments		p <sup>c</sup>
	n = 366 <sup>a</sup>		Yes, n = 38 <sup>a</sup>	No, n = 328 <sup>a,b</sup>	
	n (%)	n (%)	n (%)	n (%)	
Treatment intention <sup>d</sup>					
Total <sup>i</sup>	177 (100.0)	7 (100.)	170 (100.0)		
Curative	125 (70.6)	4 (57.1)	121 (71.2)		0.424
Palliative	52 (29.4)	3 (42.9)	49 (28.8)		
Response to treatment <sup>d</sup>					
Total <sup>i</sup>	177 (100.0)	7 (100.0)	170 (100.0)		0.209
CR	128 (72.3)	4 (57.1)	124 (72.9)		
PR	7 (3.9)	0 (0.0)	7 (4.1)		
SD	24 (13.5)	3 (42.9)	21 (12.4)		
PD	5 (2.8)	0 (0.0)	5 (2.9)		
Not yet known	13 (7.3)	0 (0.0)	13 (7.6)		

<sup>a</sup>The total number of participants in each group was set to 100 %.

<sup>b</sup>The subgroup of participants who did not postpone or miss appointments included n = 7 patients who did not have any melanoma-related appointments scheduled during the pandemic.

<sup>c</sup>Differences between the subgroups with and without appointment changes were tested for significance using Chi-square test.

<sup>d</sup>Melanoma therapies received between 01 Mar 2020 and study participation (01 Mar–30 Apr 2021).

<sup>e</sup>Other treatments comprised talimogene laherparepvec injections (n = 1), treatment within a clinical trial (n = 3) and alternative healing methods (n = 1).

<sup>f</sup>Missing data: primary melanoma surgery n = 1, systemic treatment n = 1.

<sup>g</sup>61 patients obtained monotherapy with PD-1 inhibitors, 6 nivolumab combined with ipilimumab.

<sup>h</sup>8 patients received dabrafenib and trametinib, 7 encorafenib and binimetinib, and 3 monotherapy with a BRAF- or MEK-inhibitor.

<sup>i</sup>Percentages refer to all patients who received treatment during the pandemic (n = 177, n = 7 or n = 170, 100 %). Significant findings are highlighted in italic.

Abbr.: AJCC, American Joint Committee on Cancer; CLND, complete lymph node dissection; CR, complete response; ICI, immune checkpoint inhibitors; n, number; PD, progressive disease; PR, partial response; SD, stable disease; SLNB, sentinel lymph node biopsy.

patients should not differ significantly from established standards, but decisions should be made considering the local epidemiological circumstances [9, 21]. The rate of hospital admissions should be kept as low as possible to save resources and reduce the risk of nosocomial SARS-CoV-2 infections. Treatments with a low risk of hospitalization due to toxicity should be preferred, if feasible. Regarding immune checkpoint inhibitor (ICI) therapy, the schedule with the longest approved treatment intervals should be favored [7–9, 24]. As for targeted therapy, the combination of encorafenib and binimetinib may be considered due to a lower rate of fever as adverse event imitating COVID-19 [9, 24]. Furthermore, current reports underline the supportive role of telemedicine and its significant part in delivering medical care in times of deficient health care resources [3, 9, 11, 20, 23].

Since the impact of systemic cancer treatment on viral infections remains a matter of discussions [10, 25–27], it is being evaluated if systemic melanoma therapies could represent an additional risk factor for COVID-19 and severe disease courses [27, 28]. According to data from registries and large retrospective studies, patients treated with ICIs who contracted SARS-CoV-2 infections did not have worse outcome than other oncological patients [10, 25, 29, 30]. A study examining the association between SARS-CoV-2 infections and targeted therapy in Turin, Italy expressed support for its initiation and/or continuation under strict monitoring of clinical symptoms [26]. Considering the favorable impact of adjuvant and palliative melanoma therapy on survival, these treatments must not be withheld from patients who require them during the pandemic.



**Table 3** Impact of the COVID-19 pandemic in the whole cohort and in subgroups with and without appointment changes.

Characteristic	Whole cohort		Postponed/missed appointments		p <sup>c</sup>		
	n = 366 <sup>a</sup>		Yes, n = 38 <sup>a</sup>			No, n = 328 <sup>a,b</sup>	
	n (%)		n (%)			n (%)	
SARS-CoV-2 infections <sup>d</sup>							
Patient							
No	360 (98.4)		38 (100.0)		322 (98.2)		0.401
Yes	6 (1.6)		0 (0.0)		6 (1.8)		
Outpatient treatment	3 (0.8)		0 (0.0)		3 (0.9)		
Inpatient treatment	1 (0.3)		0 (0.0)		1 (0.3)		
ICU treatment	1 (0.3)		0 (0.0)		1 (0.3)		
Household members							
No	359 (98.1)		38 (100.0)		321 (97.7)		0.363
Yes	7 (1.9)		0 (0.0)		7 (2.1)		
Outpatient treatment	6 (1.6)		0 (0.0)		6 (1.8)		
Inpatient treatment	1 (0.3)		0 (0.0)		1 (0.3)		
ICU treatment	0 (0.0)		0 (0.0)		0 (0.0)		
Close acquaintances							
No	251 (68.6)		23 (60.5)		228 (69.5)		0.259
Yes	115 (31.4)		15 (39.5)		100 (30.5)		
Outpatient treatment	83 (22.7)		13 (34.2)		70 (21.3)		
Inpatient treatment	16 (4.4)		1 (2.6)		15 (4.5)		
ICU treatment	9 (2.5)		1 (2.6)		8 (2.4)		
Unknown	7 (1.9)		0 (0.0)		7 (2.1)		
Concern about COVID-19 <sup>d</sup>							
Scale 0–100							
Mean (SD)	45.1 (27.9)		48.8 (30.8)		44.7 (27.5)		0.409
Median (IQR, range)	50.0 (50, 0–100)		50.0 (60, 0–100)		50.0 (50, 0–100)		
Concern about melanoma <sup>d</sup>							
Scale 0–100							
Mean (SD)	40.4 (28.9)		36.2 (30.4)		40.8 (28.7)		0.276
Median (IQR, range)	40.0 (47, 0–100)		20.0 (44.3, 5–100)		40.0 (45, 0–100)		
Social contact reduction							
Little	20 (5.5)		3 (7.9)		17 (5.2)		0.321
Some	38 (10.4)		1 (2.6)		37 (11.3)		
Much	106 (29.0)		10 (26.3)		96 (29.3)		
Very much	202 (55.2)		24 (63.2)		178 (54.3)		
Professional contact reduction							
Total <sup>e</sup>	100 (100.0)		9 (100.0)		91 (100.0)		

Continued

Table 3 Continued.

Characteristic	Whole cohort		Postponed/missed appointments		p <sup>c</sup>
	n = 366 <sup>a</sup>		Yes, n = 38 <sup>a</sup>	No, n = 328 <sup>a,b</sup>	
	n (%)	n (%)	n (%)	n (%)	
Little	35 (35.0)	2 (22.2)	33 (36.3)	0.777	
Some	17 (17.0)	2 (22.2)	15 (16.5)		
Much	14 (14.0)	2 (22.2)	12 (13.2)		
Very much	34 (34.0)	3 (33.3)	31 (34.1)		
Concern to continue treatment					
Total <sup>e</sup>	85 (100.0)	4 (100.0)	81 (100.0)		
None or little	73 (85.9)	2 (50.0)	71 (87.7)	0.006	
Some	10 (11.8)	1 (25.0)	9 (11.1)		
Much or very much	2 (2.3)	1 (25.0)	1 (1.2)		
Willingness to be vaccinated against COVID-19					
Yes	328 (89.6)	34 (89.5)	294 (89.6)	0.446	
No	10 (2.7)	0 (0.0)	10 (3.0)		
Undecided	28 (7.7)	4 (10.5)	24 (7.3)		

<sup>a</sup>The total number of participants in each group was set to 100 %.

<sup>b</sup>The subgroup of participants who did not postpone/miss appointments included n = 7 patients who did not have any melanoma-related appointments during the pandemic.

<sup>c</sup>Differences between the subgroups that did or did not change appointments were tested for significance with Chi-square test for binary and categorical variables and with Mann-Whitney-U test for linear variables.

<sup>d</sup>Missing data: Treatment setting of the SARS-CoV-2 infection of a study participant n = 1; concern about COVID-19 n = 4; concern about melanoma n = 3.

<sup>e</sup>Percentages refer to all patients who provided information about professional contact reduction (n = 100, n = 9 or n = 91, 100 %) and concern to continue treatment (n = 85, n = 4 or n = 81, 100 %).

Significant findings are highlighted in italic.

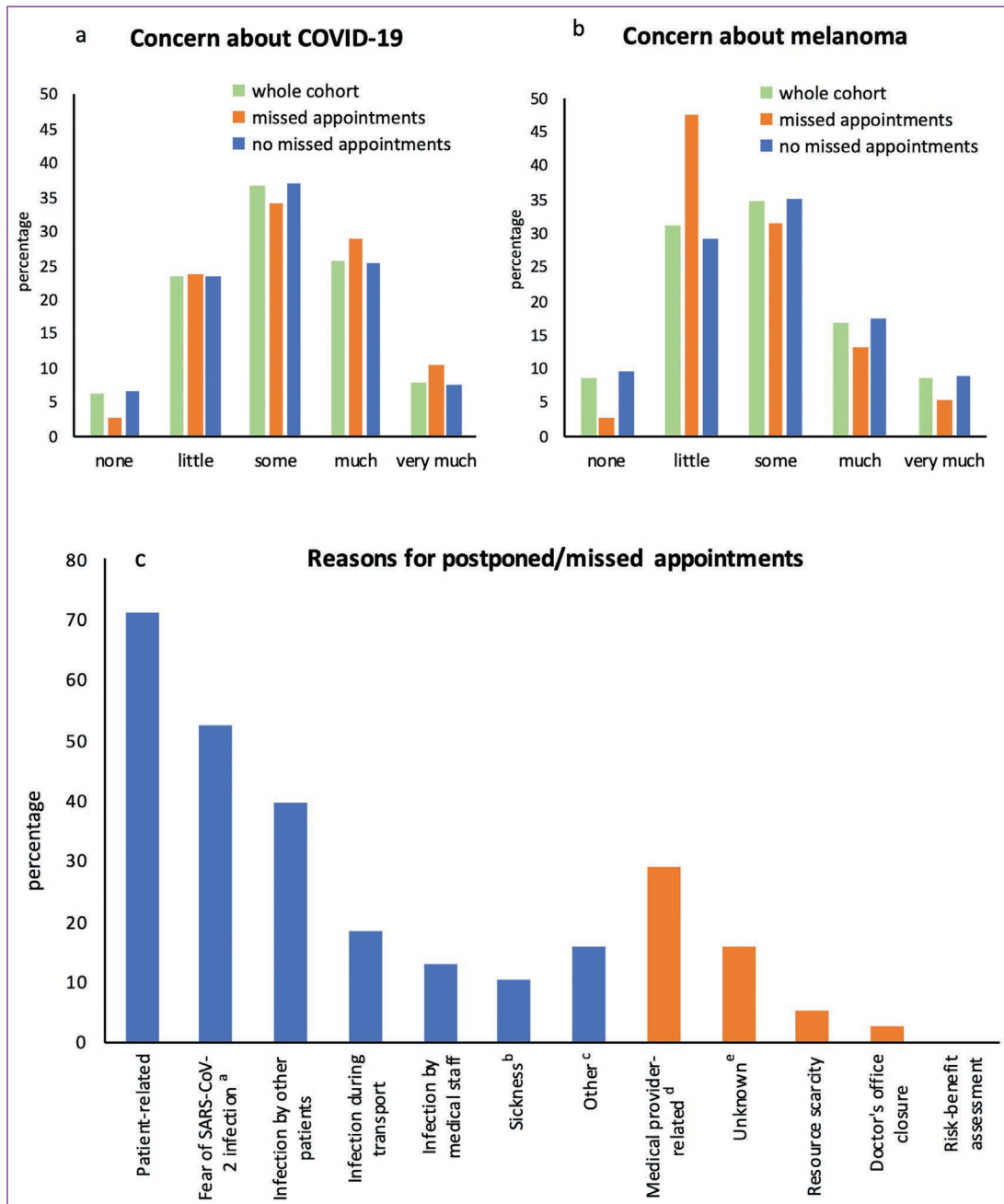
Abbr.: ICU, intensive care unit; IQR, Interquartile range; n, number; SD, standard deviation

### Appointment changes during the pandemic

Only 10.1 % of our participants experienced appointment changes, the vast majority of which were follow-up visits. A more significant decrease in melanoma follow-up visits was reported in other countries and regions such as in Padua in Northern Italy (30.2 % during the first wave [31]) and in the USA (23.2 % [32]). Indeed, the Italian and US American health care systems were more severely strained by COVID-19 than the German one, particularly during the first wave. However, findings also vary among German skin cancer centers depending on the local epidemiological situation. In Dortmund, no significant decrease in follow-up appointments was noted [33], whereas in Munich, the cancellation rate of skin cancer appointments was 12.0 % higher during the first wave compared to 2019 [18].

In our study and in the precedent Mela-COVID survey [21], reasons for cancellations of melanoma-related appointments were assessed in greater detail than in other studies. The most common reason was patients' fear about COVID, well in accordance with data from an Italian WhatsApp messenger-based survey [34] and with hypotheses discussed by others [18, 33].

Participants of our cohort currently receiving treatment as well as those with present tumor burden were less likely to miss appointments, suggesting that they understood the importance of continuing therapy and the potentially severe consequences of neglecting cancer care. On the other hand, increasing age, higher education and longer disease duration predicted a higher probability of missing appointments, possibly because patients with these characteristics feared nosocomial SARS-CoV-2 infections more than a potentially



**Figure 3** Concern about COVID-19 (a) and melanoma (b) in the whole cohort and in subgroups that did or did not postpone or miss appointments. The total number of patients in each subgroup was set to 100 %. Reasons for changed appointments (c). The total number of patients with postponed or missed appointments (n = 38) was set to 100 %.

<sup>a</sup>Percentages do not sum up to 100 % because 5 patients provided more than one answer.

<sup>b</sup>Other sickness than a SARS-CoV-2 infection.

<sup>c</sup>Other reasons were stated by 7 patients and specified as free text by 4 of them. The first patient postponed his appointment because his wife was sick, the second had another surgery planned, the third did not find the visit necessary and the fourth was afraid of an insufficient standard of hygiene.

<sup>d</sup>Out of 11 appointment changes due to medical provider-related reasons, 5 occurred in the Vivantes Skin Cancer Center and 6 in external dermatological practices.

<sup>e</sup>Reasons for medical-provider-related appointment changes could not be recapitulated in 6 cases, among these 3 at the Vivantes Skin Cancer Center and 3 in external dermatological practices.

**Table 4** Multivariate logistic regression analysis of impact factors on postponed or missed appointments.

Characteristic	OR <sup>a</sup>	95 % CI	p
Female	1.056	0.470–2.372	0.895
Age	1.037	1.002–1.074	0.039
AJCC stage			
II	1.616	0.619–4.221	0.327
III	1.735	0.551–5.467	0.346
IV	1.521	0.352–6.556	0.574
Current treatment <sup>b</sup>	0.194	0.070–0.542	0.002
≥ 5 comorbidities	0.681	0.291–1.596	0.377
Concern about COVID-19 <sup>c</sup>	1.581	0.981–2.548	0.060
Concern about melanoma <sup>c</sup>	0.771	0.476–1.249	0.291
Disease duration <sup>d</sup>	1.007	1.001–1.013	0.028
High school degree <sup>e</sup>	2.263	1.025–4.996	0.043

<sup>a</sup>Postponed/missed appointment was defined as the dependent variable. Sex, age, AJCC 2017 stage, current treatment, ≥ 5 comorbidities, concern about COVID-19, concern about melanoma, disease duration and school degree were integrated into the model as independent variables. Reference categories were male, AJCC stage I, no current treatment, < 5 comorbidities and low/intermediate school degree. Age, concern about COVID-19 and concern about melanoma were integrated as linear variables.

<sup>b</sup>Current treatment comprised all melanoma therapies received from 01 March 2020 until study participation (01 Mar–30 Apr 2021).

<sup>c</sup>Concern about COVID-19 and melanoma was indicated on a scale from 0 (no concern) to 100 (highest concern).

<sup>d</sup>In months.

<sup>e</sup>A-levels (“Abitur” or “Fachabitur”).

Significant findings are highlighted in italic.

Abbr.: AJCC, American Joint Committee on Cancer; CI, confidence interval; OR, odds ratio.

negative impact of skipped appointments on their melanoma disease.

### Appointment changes during first pandemic wave and thereafter

In the Mela-COVID study conducted immediately after the first COVID-19 wave, 14.8 % of the participants (i.e., 48 of 324) postponed or missed appointments [21]. Interestingly, the proportion of appointment changes recorded in the present study was lower, even if the time span covered was longer and the incidence of COVID-19 in Germany was significantly higher in winter and spring 2021 compared to spring 2020. Despite high numbers of patients with COVID-19 in our hospitals and ICUs during the second and third wave, we managed to maintain guideline-conform melanoma care under intensive safety measures [5] and thanks to progress of the vaccination campaign.

Compared to the Mela-COVID study, participants of the present study were more concerned about COVID-19 and reduced their social contacts more, but did not miss their appointments more often. In the Mela-COVID study, concern about COVID-19, anxiety disorder and SARS-CoV-2 infections among close acquaintances appeared as significant risk factors for appointment changes [21], whereas after one year of pandemic these factors did not seem to be decisive for changes anymore. This indicates that, despite greater concern about COVID-19, patients have learned to cope with the pandemic and understood that they must not neglect their melanoma disease meanwhile, especially because the duration of the pandemic remains unknown. During its first wave there was hope that it would soon be overcome, but two years later it is evident that we are facing a long-term problem. Meantime, patients and medical staff adapted to the challenging reality, in order to obtain and provide the best possible melanoma care under extensive precautions.

**Table 5** Pandemic-related impairment of the subcohort that participated both in the Mela-COVID study in May-June 2020 and in the Mela-COVID Follow-up study.

Characteristic	During one year of pandemic <sup>a</sup>	During first wave <sup>b</sup>	After first wave <sup>c</sup>	p <sup>d</sup>
	n = 216	n = 216	n = 216	
	n (%)	n (%)	n (%)	
Changed/postponed treatment <sup>e</sup>	2 (0.9)	2 (0.9)	0 (0.0)	n.d. <sup>g</sup>
Missed/postponed appointments <sup>e,f</sup>	45 (20.8)	29 (13.4)	19 (8.8)	0.741
SARS-CoV-2 infections <sup>e</sup>				
Patient	5 (2.3)	1 (0.5)	5 (2.3)	0.023
Outpatient treatment	3 (1.4)	0 (0.0)	3 (1.4)	
Inpatient treatment	1 (0.5)	1 (0.5)	1 (0.5)	
ICU treatment	1 (0.5)	0 (0.0)	1 (0.5)	
Household members	5 (2.3)	1 (0.5)	5 (2.3)	0.023
Outpatient treatment	5 (2.3)	1 (0.5)	5 (2.3)	
Inpatient treatment	0 (0.0)	0 (0.0)	0 (0.0)	
ICU treatment	0 (0.0)	0 (0.0)	0 (0.0)	
Close acquaintances	64 (29.6)	11 (5.1)	64 (29.6)	< 0.001
Outpatient treatment	47 (21.8)	8 (3.7)	47 (21.7)	
Inpatient treatment	8 (3.7)	3 (1.4)	8 (3.7)	
ICU treatment	5 (2.3)	0 (0.0)	5 (2.3)	
Treatment not known	4 (1.8)	0 (0.0)	4 (1.8)	
Concern about COVID-19 <sup>e</sup>				
Scale 0–100				
Mean (SD)	42.9 (28.3)	35.3 (27.0)	42.9 (28.3)	< 0.001
Median (IQR, range)	48.5 (50, 0–100)	30 (40, 0–100)	48.5 (50, 0–100)	
Concern about melanoma <sup>e</sup>				
Scale 0–100				
Mean (SD)	35.8 (27.9)	37.8 (27.3)	35.8 (27.9)	0.181
Median (IQR, range)	30.0 (40, 0–100)	35 (50, 0–100)	30.0 (40, 0–100)	
Social contact reduction <sup>e</sup>				
Little <sup>h</sup>	13 (6.0)	28 (13.2)	13 (6.0)	0.001
Some	26 (12.0)	26 (12.2)	26 (12.0)	
Much	63 (29.2)	76 (35.2)	63 (29.2)	
Very much	114 (52.8)	83 (38.4)	114 (52.8)	
Professional contact reduction <sup>i</sup>				
Little <sup>h</sup>	17 (34.0)	15 (32.6)	17 (34.0)	0.865
Some	10 (20.0)	7 (15.2)	10 (20.0)	
Much	7 (14.0)	7 (15.2)	7 (14.0)	
Very much	16 (32.0)	17 (37.0)	16 (32.0)	

Continued

Table 5 Continued.

Characteristic	During one year of pandemic <sup>a</sup>	During first wave <sup>b</sup>	After first wave <sup>c</sup>	p <sup>d</sup>
	n = 216	n = 216	n = 216	
	n (%)	n (%)	n (%)	
Concern to continue treatment <sup>f</sup>				
None or little	33 (68.8)	71 (63.4)	33 (68.8)	0.954
Some	11 (22.9)	34 (30.3)	11 (22.9)	
Much or very much	4 (8.3)	7 (6.2)	4 (8.3)	

<sup>a</sup>From 01 Mar 2020 until the date of participation in the Mela-COVID Follow-up study (01 Mar–30 Apr 2021).

<sup>b</sup>From 01 Mar 2020 until 30 Jun 2020, i.e. in the time span covered by the Mela-COVID study.

<sup>c</sup>After 30 Jun 2020 until the date of participation in the Mela-COVID Follow-up study.

<sup>d</sup>Impairment by the pandemic during and after the first wave, i.e. when answering the Mela-COVID and the Mela-COVID Follow-up survey, was compared with Chi-square test for binary and categorical variables, with Fisher's exact test for subgroups with small numbers and with Wilcoxon-Test for linear variables.

<sup>e</sup>Missing data during the first wave (Mela-COVID study): treatment changes n = 2, appointment changes n = 1, SARS-CoV-2 infections of close acquaintances n = 1, concern about COVID-19 n = 6, concern about melanoma n = 1, social contact reduction n = 3. Missing data in the Mela-COVID Follow-up study: concern about COVID-19 n = 2, concern about melanoma n = 1.

<sup>f</sup>3 patients postponed their appointments both during the first wave and thereafter.

<sup>g</sup>n.d.: not determined due to sample size.

<sup>h</sup>The category comprises the answers "not at all" and "little" in the Mela-COVID study.

<sup>i</sup>Information on professional contact reduction was provided by 46 participants in the Mela-COVID study and by 50 participants in Mela-COVID Follow-up study.

<sup>j</sup>Information on concern to continue treatment was provided by 112 patients in the Mela-COVID study and by 48 patients in the Mela-COVID Follow-up study.

Significant findings are highlighted in italic.

## Vaccination

Less than one year after the pandemic outbreak, several COVID-19 vaccines were developed which significantly reduce the risk of SARS-CoV-2 infections and severe COVID-19 courses and give reason to great hope in the fight against the pandemic [35–37]. As shown in reports from Poland and France, cancer patients tend to present a positive attitude towards COVID-19 vaccination [38, 39]. The same finding was made in our study, in which almost 90 % of the participants declared their willingness to be vaccinated. Patients with active melanoma are considered a risk group and were therefore prioritized in the German COVID-19 vaccination campaign [40].

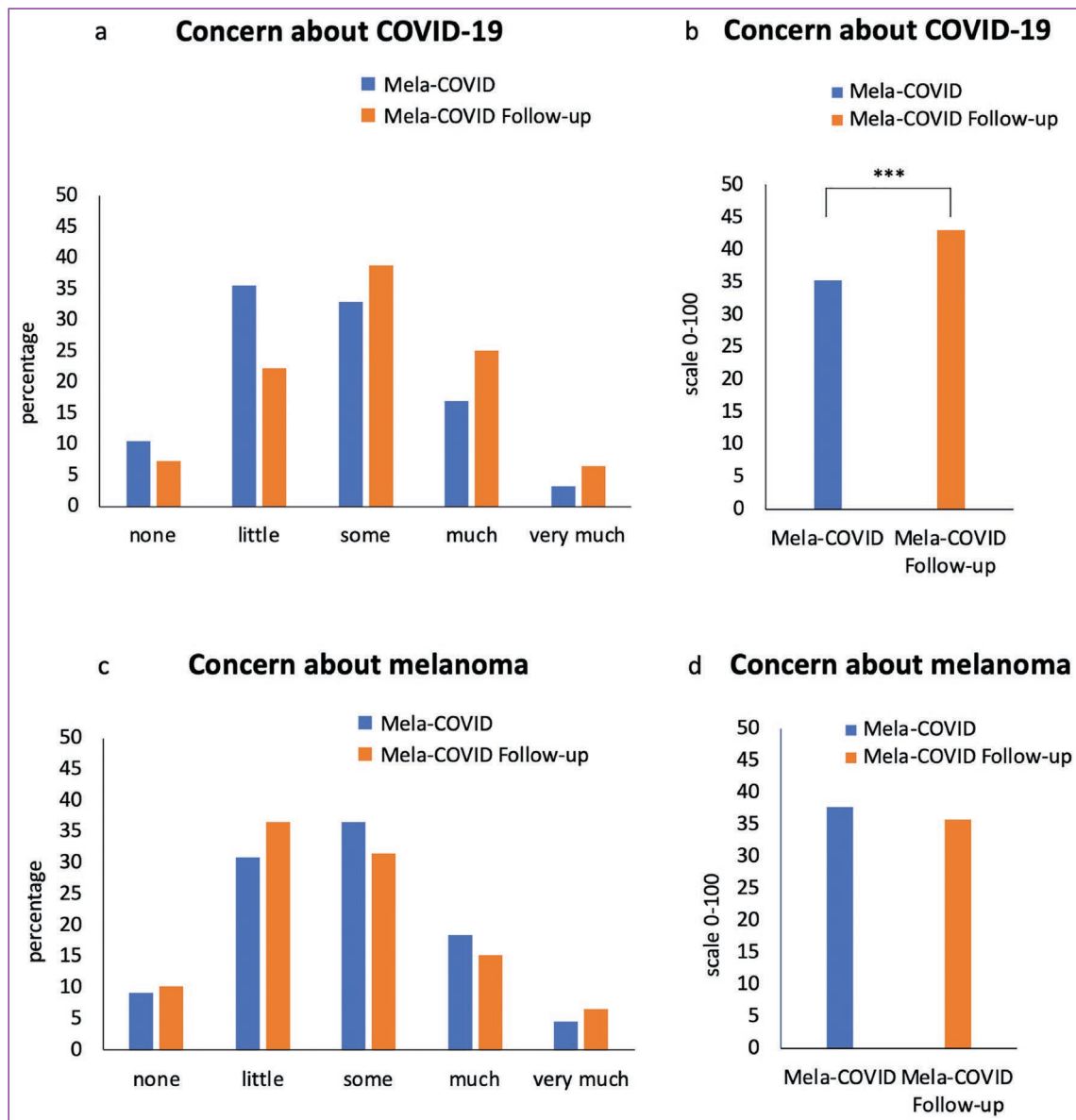
## Limitations

The size of our cohort was limited, and data were collected exclusively in Berlin. Our findings may not be representative for all melanoma patients from our center due to selection bias. Compared to non-responders, the study cohort was on average older, contained a higher proportion of males and received treatment during the pandemic more frequently.

On the one hand, increasing age correlated with a higher probability of missing appointments. On the other, current treatment strongly predicted adherence to appointments, suggesting that rates of appointment changes may have been higher among non-responders. As information was collected retrospectively, some participants had probably forgotten changes that occurred early during the pandemic. The time of treatment changes was documented in the medical records, but the exact time of appointment changes was not recorded.

## Conclusions

Neglecting cancer care as a collateral damage of the pandemic has to be absolutely avoided, and the importance of maintaining regular treatment and follow-up schedules for melanoma patients cannot be underestimated. Our study showed only few pandemic-related treatment changes and a relatively low rate of skipped appointments. While patients' concern about COVID-19 was higher after the second than after the first wave of the pandemic, the rate of cancelled appointments tended to be lower, indicating that patients



**Figure 4** Concern about COVID-19 (a, b) and melanoma (c, d) in five categories (a, c) and on a 0–100 scale (b, d) in the sub-cohort that participated both in the Mela-COVID and in the Mela-COVID Follow-up study. Participants were significantly more concerned about COVID-19 after one year of pandemic (Mela-COVID Follow-Up) than after its first wave (Mela-COVID;  $p < 0.001$  both when comparing concern in 5 categories and on a 0–100 scale). Concern about melanoma did not differ significantly at both times. \*\*\*  $p = 0.001$ .

adapted to guideline-conform melanoma care under novel circumstances and gained trust in the safety measures implemented to prevent nosocomial SARS-CoV-2 infections.

**Conflict of interest**

AM participated in clinical trials for Novartis and Sanofi and obtained financial support for participation in conferences from LEO Pharma and Mylan. BS participated in clinical tri-

als from Array Biopharma, Janssen-Cilag, MSD and Sandoz and obtained financial support for participation in conferences from Janssen-Cilag. JO served as investigator for Novartis and received financial support for participation in conferences from Novartis, Merck und Pierre-Fabre. GB served as investigator for Novartis and Pfizer, was member of advisory boards of Novartis, BMS and Leo Pharma and received financial support for participation in conferences from Novartis, Pierre-Fabre and



Merck Serono. FK was member of advisory boards from Amgen, Bristol-Myers Squibb (BMS), Roche, Novartis, MSD and Sanofi. UH served as investigator for Magnosco and Novartis, was member of advisory boards of Novartis and Takeda, obtained honoraria from AbbVie, Novartis and OmniaMed, and received support for conferences from Almirall Hermal, Amgen, Biofrontera, BMS, L'Oréal, MSD, Novartis, Roche, Pierre Fabre and Takeda. WH was member of advisory boards of Novartis, obtained honoraria from Novartis and LEO Pharma, and received support for conferences from Abbvie, Almirall Hermal, Beiersdorf, Dermo Medical, Biofrontera, Celgene, Dermapharm, Dr. Pflieger, Galderma, Hexal, Janssen-Cilag, Jenapharm, Kosmetik vom Wasserfall, LEO Pharma, Medac, Novartis and Pfizer. WKP served as investigator for AbbVie, Array Biopharma, Boehringer Ingelheim, Eli Lilly, Janssen-Cilag, MSD, Novartis, Pfizer and UCB Pharma, was member of advisory boards of BMS, Eli Lilly, LEO Pharma, MSD, Novartis, Pfizer, Roche, Sanofi and UCB Pharma, obtained honoraria from ALK-Abello, AbbVie, Biotest, BMS, Janssen-Cilag, MSD, Novartis, Pfizer, Dr. Pflieger and Roche, and received support for conferences from AbbVie, Actelion, ALK-Abello, Alma Lasers, Almirall Hermal, ARC Lasers, Asclepion, Beiersdorf, BMS, Celgene, Dermapharm, Dermasence, Eli Lilly, Galderma, GSK, Immunocore, Janssen-Cilag, L'Oréal, La Roche Posay, LEO Pharma, Medac, MSD, Mylan, Novartis, Pierre Fabre, P&M Cosmetics, Pfizer, Roche, Sanofi and Sun Pharma. KD, MT and M-LS declare no conflict of interest relevant for this manuscript. The study was performed without the support of the pharmaceutical industry, and the conflicts of interest have no impact on the content of the manuscript.

### Correspondence to

Wiebke K. Ludwig-Peitsch, MD  
Department of Dermatology and Phlebology  
Vivantes Klinikum im Friedrichshain

Landsberger Allee 49  
10249 Berlin, Germany

E-mail: wiebke.ludwig-peitsch@vivantes.de

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