Ocular Oncology and Pathology

Research Article

Ocul Oncol Pathol
DOI: 10.1159/000524918

Received: January 23, 2022
Accepted: April 22, 2022
Published online: May 9, 2022

Comparison of Tumor Size and Gene Expression at Presentation in Uveal Melanoma Patients before and during the COVID-19 Pandemic

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Keywords
Ocular oncology · Uveal melanoma · COVID-19 pandemic

Abstract
Introduction: The aim of this study was to compare the clinical and gene expression variables of uveal melanoma patients presenting before and after the start of the COVID-19 pandemic as surrogate markers in order to assess the pandemic's potential impact on care. ***Methods:*** We conducted a retrospective chart review of uveal melanoma patients at Retina Consultants of Texas and assessed tumor size, staging, and gene expression data during two time periods: May 2019 to February 2020 (Group 1: Before the COVID-19 pandemic declaration by the WHO in March 2020) and May 2020 to March 2021 (Group 2: After the start of the COVID-19 pandemic). ***Results:*** A total of 80 patients with uveal melanoma were studied (Group 1: 40 [50%] and Group 2: 40 [50%]). There was no statistically significant difference in the tumor thickness ($p = 0.768$), largest base dimension ($p = 0.758$), Collaborative Ocular Melanoma Study size class ($p = 0.762$), and American Joint Committee on Cancer stages ($p = 0.872$) between the two groups. Additionally, there was no difference in the tumors' gene expression data including gene expression profile class ($p = 0.587$) and PRAME expressivity ($p = 0.861$) between the two groups. ***Discussion/Conclusion:*** The COVID-19 pandemic had no effect on the presentation of uveal melanoma patients across all tumor characteristics including size, staging, and gene expression data, suggesting there was not a significant diagnostic delay in care for uveal melanoma patients at our center due to the pandemic.

Introduction

Two years into the COVID-19 pandemic, hundreds of thousands of patients have died of the disease, and numerous economic, social, and health-care related indirect casualties have emerged. One major effect of the pandemic has been a delay in presentation and interruptions in delivery of care to patients with many different cancer types, including lung, breast, prostate, ovarian, and others [1–5].

Uveal melanoma is the most common primary intraocular malignancy among adults. Survival after 15 years is 50% and development of metastasis significantly increases mortality with 1 year survival of approximately

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15% [6, 7]. Given the poor prognosis of patients with metastatic uveal melanoma, early detection and treatment initiation is crucial. Unfortunately, ophthalmology and ocular oncology clinics have not been spared the consequences of the pandemic. The decreased number of patients presenting to clinics and hospitals with ophthalmic conditions has raised concerns that patients are avoiding or unable to access medical care for potentially sight-threatening conditions [8]. For example, studies have shown patients presenting with retinal detachments during the pandemic era have increased rates of macular detachments and worse baseline visual acuity at presentation [9, 10]. In ocular oncology, one center in India has demonstrated that the coronavirus lockdown has caused significant delays and interruptions in the treatment of children with retinoblastoma [5]. Our study aimed to analyze the size, prognostic stage, and gene expression of tumors of uveal melanoma patients presenting before and after March 2020 in order to assess a possible delay in care due to the COVID-19 pandemic.

Materials and Methods

Study Design and Data Collection

We conducted a retrospective matched cohort study of patients treated with uveal melanoma at Retina Consultants of Texas during two time periods: May 2019 to February 2020 (Group 1: before the COVID-19 pandemic declaration by the WHO in March 2020) and May 2020 to March 2021 (Group 2: after the start of the COVID-19 pandemic). We selected May 2020 as the start of the pandemic study period since we hypothesized that we would begin to see a possible effect on tumor size due to presentation delay. For the end of the study period for Group 2, we selected March 2021, when the vaccine became available for all adults in Texas. We had 40 patients in the selected time period of May 2020 to March 2021 for Group 2 and selected a matched cohort (40 patients) in the period prior to the pandemic (before February 2020) based on age and sex.

Patients with uveal melanoma of the choroid, ciliary body, or iris were consecutively selected from these time periods and included in the study. Patients less than 18 years old and with insufficient data for primary objectives (size, staging, and genetic expression) on chart review were excluded from this study. Patients from the two groups were matched based on age and sex. We accessed records of patients eligible for study via the institution's electronic health record and collected size, staging, and gene expression data of the tumors at presentation. We assessed the size of the tumors by utilizing the largest basal dimension and tumor thickness by ultrasound and assigning a size classification established by the Collaborative Ocular Melanoma Study (COMS) and the American Joint Committee on Cancer (AJCC). The COMS size classification characterizes tumors 1.5–2.4 mm in height and 5–16 mm in diameter as small, 2.5–10 mm in height and ≤16 mm in diameter as medium, and >10 mm in height or 8–10 mm in height in proximity to optic nerve or >16 mm in diameter as large [11]. AJCC stages (I, IIA, IIB, IIIA, IIIB, IIIC, or IV) were defined in accordance with the TNM (tumor size, node, and metastasis) prognostic stage classification from the 8th edition of the AJCC Cancer Staging Manual [7]. We used the commercially available gene expression profile (GEP) test, an RNA-based assay assessing the expression of 12 experimental and 3 control genes to stratify tumors based on metastatic risk (Castle Biosciences, Friendswood, TX, USA). We also collected data on PRAME expression (preferentially expressed antigen in melanoma) status to determine tumors' metastatic risk (Castle Biosciences). GEP 5-year metastatic potential is stratified into Classes 1A (low), 1B (intermediate), and 2 (high). Tumors were identified as having a positive or negative PRAME expression. Additionally, given the pandemic's impact on travel, we analyzed the distance patients travelled (from their home city) to Houston (location of the Retinal Consultants of Texas Clinic). Distances were stratified by travel less than 50 km, between 50 and 200 km, between 200 and 400 km and greater than 400 km.

Statistical Analysis

Data were summarized as mean (standard deviation) for continuous variables and frequency (%) for discrete variables. Two-sample t test was used to analyze continuous variables and χ^2 test was used for categorical variables to compare the outcomes between the pre- and during COVID period. Statistical analyses were performed using Mathworks MATLAB. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 80 patients with uveal melanoma were studied (Group 1: 40 [50%] and Group 2: 40 [50%]; mean age: 62.5 years [range 25–84] and 64 years [range 30–91]). The characteristics of the tumors in each group are listed in Table 1. There was no statistically significant difference between the tumor thickness, largest base dimension, and COMS size class between Group 1 (pre-COVID) and Group 2 (during COVID). The majority of patients were found to be in AJCC class I/IIA in both groups (Group 1: 26 [65%] and Group 2: 27 [67.5%]), with no statistically significant difference in staging between the groups. Analyzed gene expression data of GEP class and PRAME expression also failed to show a difference between Group 1 and Group 2, with the majority of patients found to be GEP Class IA (Group 1: 27 [69.2%] and Group 2: 25 [62.5%]) and PRAME negative (Group 1: 28 [71.8%] and Group 2: 28 [70%]) for both groups. There was no statistically significant difference in the distances travelled by patients to the clinic before and during the pandemic. The majority of patients were living within a 200 km radius of Houston (Group 1: 25 [62.5%] and Group 2: 26 [65%]).

Table 1. Characteristics of patients in the study

Characteristic	Group 1 pre-COVID *N* = 40	Group 2 during COVID *N* = 40	*p* value
Age, years	62 (25–84)	64 (30–91)	0.716*
Gender, *n* (%)			
Male	22 (55)	19 (47.5)	0.502†
Female	18 (45)	21 (52.5)	
Distance, km, *n* (%)			
<50	20 (50)	15 (37.5)	0.386†
50–200	5 (12.5)	11 (27.5)	
200–400	8 (20)	7 (17.5)	
≥400	7 (17.5)	7 (17.5)	
Tumor thickness, mm	4.3 (1.4–10.6)	4.5 (1.2–15)	0.768*
Largest base dimension, mm	12.6 (5.5–24)	13.1 (5.5–32)	0.758*
COMS size, *n* (%)			
Small	16 (40)	15 (37.5)	0.762†
Medium	14 (35)	17 (42.5)	
Large	10 (25)	8 (20)	
AJCC stages, *n* (%)			
I	17 (42.5)	17 (42.5)	0.872†
IIA	9 (22.5)	10 (25)	
IIB	6 (15)	7 (17.5)	
IIIA	5 (12.5)	3 (7.5)	
IIIB	3 (7.5)	2 (5)	
IIIC	0 (0)	1 (2.5)	
IV	0 (0)	0 (0)	
GEP class, *n* (%)			
1A	27 (69.2)	25 (62.5)	0.587†,¶
1B	3 (7.7)	6 (15)	
2	9 (23)	9 (22.5)	
PRAME expression, *n* (%)			
Positive	11 (28.2)	12 (30)	0.861†,¶
Negative	28 (71.8)	28 (70)	

* Two sample *t* test. † χ^2 test. ¶ One patient in Group 1 did not have satisfactory data for gene expression variables GEP class and PRAME expression so was excluded from gene expression comparison between the groups.

Discussion

Strict and timely responses to the COVID-19 pandemic in the form of reduced capacity in clinics and cancelled procedures/surgeries have led to unintended consequences in cancer care [1–5]. The degree of impact from the pandemic appears to vary depending on the cancer type. Our study showed that the COVID-19 pandemic had no effect on the presentation of uveal melanoma patients at our center across various tumor characteristics that can be used as a surrogate marker for delayed presentation, including size, staging, and gene expression data.

One explanation for the lack of diagnostic delay during the pandemic may be that a significant proportion of uveal melanoma patients (30%) are asymptomatic. Thus, many uveal melanoma cases are not diagnosed until advanced enough to cause symptoms, making early detection difficult regardless of any delays in care caused by the pandemic [12]. We considered analyzing the length of time from initial symptoms to presentation in the clinic as another possible surrogate marker for delay in care. However, many of the patients in the study were found to be asymptomatic or had nonspecific symptoms (e.g., blurry vision in both eyes), making it difficult to distinguish which symptoms could be directly attributed to the uveal melanoma.

In general, there is a complex interplay between geographic and socioeconomic factors in determining the pandemic's impact on a certain population [13]. Patients who live in or in proximity to a metropolitan area like

Houston, TX (location of our study) have a significant advantage over patients that live in rural areas in terms of access to healthcare, especially for highly subspecialized services such as ocular oncology. We found in our study that the majority of our patients lived within a 200 km radius of Houston (approximately 2 h car travel time), allowing them to avoid plane travel during the start of the pandemic when flights were limited and avoided. These advantages may have allowed patients timely access to healthcare for diseases such as uveal melanoma and thus prevented diagnostic delays even during the start of the pandemic. Further studies on the impact of the pandemic on uveal melanoma patients in rural areas need to be conducted to elucidate these geographic differences.

A similar study was conducted in 2021 by Wang et al. [14] in the form of a multi-center analysis in the United Kingdom. Their findings showed a decreased number of referrals to ocular oncology services during the COVID-19 lockdown period, with a subsequent increase in advanced uveal melanoma cases in the months following the lockdown [14]. While their study limited their analysis to AJCC staging of uveal melanoma tumors, they found a significant increase in patients with Stage III and IV cancers [14]. In comparison, our study analyzed AJCC staging as well as size and gene expression data of the tumors but showed no difference in patients presenting before and after the start of the pandemic.

The differences in outcomes could be partly attributed to the regional context of the studies, with the UK and the USA (and more specifically, Texas) having vastly different approaches to the pandemic [15]. For example, the UK had a legally enforced nationwide lockdown from March 2020 to May 2020, while the Texas government never issued a stringent lockdown order. In addition, while some ophthalmology clinics in the USA reduced patient capacity at the start of the pandemic, the vast majority did not completely close and were still available to see urgent cases. These changes were made in accordance with the American Academy of Ophthalmology statement issued in March 2020 that ophthalmologists provide only urgent or emergent care [16].

Limitations of our study include a small sample size and a short follow-up period after pandemic inception. A large-scale, long-term study is necessary to analyze the long-term consequences of the pandemic on uveal melanoma patients.

Statement of Ethics

Ethics approval was granted for this study by the institution's IRB, which did not deem written consent necessary due to this study being a retrospective review of patients' charts with no influence on treatment. The study was conducted fully in accordance with the World Medical Association of Helsinki. This study protocol was reviewed and approved by MORTI at Houston Methodist Research Institute, approval number 00019276.

Conflict of Interest Statement

The authors declare no disclosures or conflicts of interest.

Funding Sources

This study received no external funding.

Author Contributions

Amy Schefler conceived the manuscript, reviewed the data, and edited the manuscript. Naomi Hasegawa wrote the manuscript. Alexander Rusakevich and Naomi Hasegawa collected the relevant data. Bin S. Teh and Eric Bernicker reviewed the data.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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