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Changes in Cancer Management due to COVID-19 Illness in Patients with Cancer in Northern California

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QUESTION ASKED: How has a COVID-19 diagnosis in patients with cancer impacted their subsequent cancer management and care received in San Francisco Bay Area academic medical centers?

SUMMARY ANSWER: The majority of patients with cancer undergoing active management at the time of COVID-19 diagnosis had a delay in treatment, with a median duration of 21 days.

WHAT WE DID: Patients diagnosed with COVID-19 with a current or historical diagnosis of malignancy were retrospectively identified from the electronic medical record at both large academic medical centers in the San Francisco Bay Area: University of California, San Francisco, and Stanford University. The proportion of patients undergoing active cancer management whose care was affected was quantified and analyzed for significant differences with regard to management type, treatment intent, and the time of COVID-19 diagnosis.

WHAT WE FOUND: Of 55 patients undergoing active cancer management at the time of COVID-19 diagnosis, 35 (64%) had significant changes that consisted primarily of delay. An additional three patients who were not undergoing active cancer management, but were either newly diagnosed with cancer or developed recurrent cancer, experienced a delay in cancer management. The decision to change management was correlated with the time of COVID-19 diagnosis, with more delays identified in patients

managed with a palliative intent earlier in the course of the pandemic (March/April 2020) compared with later (May/June 2020) (OR, 4.2; 95% CI, 1.03 to 17.3; $P = .0497$).

BIAS, CONFOUNDING FACTOR(S): Our study is limited by sample size and clinical heterogeneity of the patient population; larger, multi-institutional studies are needed to both confirm and add to our findings. Geographically, our study population is located in the San Francisco Bay Area, and local factors including virus prevalence and the availability of hospital resources likely play a role in cancer management decisions. Moreover, longer-term follow-up is necessary to determine the full impact of these delays in care on the outcomes of patients with cancer.

REAL-LIFE IMPLICATIONS: The COVID-19 pandemic has changed many aspects of the delivery of cancer. In this manuscript, we demonstrate that the majority of COVID-affected patients with cancer undergoing active management have had a change in their care, even within an area of relatively low disease prevalence compared with other parts of the country. These delays should be considered by providers and policymakers when developing procedures governing the care of cancer patients with COVID-19. As the pandemic evolves, we will learn how changes in management and delays in treatment ultimately impact on health outcomes of patients with cancer.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and disclosures are available with the complete article at ascopubs.org/journal/op.

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abstract

PURPOSE The response to the COVID-19 pandemic has affected the management of patients with cancer. In this pooled retrospective analysis, we describe changes in management patterns for patients with cancer diagnosed with COVID-19 in two academic institutions in the San Francisco Bay Area.

MATERIALS AND METHODS Adult and pediatric patients diagnosed with COVID-19 with a current or historical diagnosis of malignancy were identified from the electronic medical record at the University of California, San Francisco, and Stanford University. The proportion of patients undergoing active cancer management whose care was affected was quantified and analyzed for significant differences with regard to management type, treatment intent, and the time of COVID-19 diagnosis. The duration and characteristics of such changes were compared across subgroups.

RESULTS A total of 131 patients were included, of whom 55 were undergoing active cancer management. Of these, 35 of 55 (64%) had significant changes in management that consisted primarily of delays. An additional three patients not undergoing active cancer management experienced a delay in management after being diagnosed with COVID-19. The decision to change management was correlated with the time of COVID-19 diagnosis, with more delays identified in patients treated with palliative intent earlier in the course of the pandemic (March/April 2020) compared with later (May/June 2020) (OR, 4.2; 95% CI, 1.03 to 17.3; $P = .0497$). This difference was not seen among patients treated with curative intent during the same timeframe.

CONCLUSION We found significant changes in the management of cancer patients with COVID-19 treated with curative and palliative intent that evolved over time. Future studies are needed to determine the impact of changes in management and treatment on cancer outcomes for patients with cancer and COVID-19.

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INTRODUCTION

Oncology practice has been transformed in response to the COVID-19 pandemic. Initial retrospective studies from China, where SARS-CoV-2 originated, suggested that patients with cancer may be more susceptible to contracting the virus partially through healthcare-related spread and have excess mortality from COVID-19 illness compared with patients without cancer.^{1,2} In response to the perceived vulnerability of patients with cancer in an acute pandemic, oncologists have postponed chemotherapy treatments, delayed curative surgeries, abbreviated radiotherapy, and switched intravenous therapies to oral therapies.³ Although there was little evidence to support these measures, protective policies were broadly used to decrease healthcare exposure among these patients who were often

immunocompromised. More recently, publication of large, prospective cohorts of patients with cancer have helped define risk factors for mortality in this patient population.^{1,4-8}

Given the uncertainty about optimal management of patients with cancer during the pandemic, guidelines based on expert consensus have been published to guide clinicians.⁹⁻¹⁶ However, during the early months of the pandemic, there was limited guidance on how to manage cancer-directed treatment for patients with COVID-19 infection,^{17,18} and oncologists had to rely on local and regional public health authorities to make recommendations to their patients. Although there have been some reports based on oncologist surveys that have revealed changes in attitudes toward therapy due to COVID-19 concerns,¹⁹⁻²⁴ to the best of our knowledge the implications of COVID-19 infection on

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the cancer-directed management of patients with cancer are unknown.

Herein, we report a pooled retrospective cohort study of patients with cancer and COVID-19 diagnosis at Stanford University (SU) and the University of California, San Francisco (UCSF), and describe the incidence, nature, and reasons for changes in cancer-directed management. We hypothesize that the incidence and duration of change in cancer management vary according to clinical factors, and that these findings will inform future oncology practice for cancer patients with COVID-19 diagnosis.

MATERIALS AND METHODS

Patient Selection

Demographic and clinical data were obtained from electronic medical records. At UCSF and SU, patients with a current or historical pathologic diagnosis of an invasive cancer were identified using the electronic medical record and the Stanford Cancer Registry, respectively. Patients must have also tested positive for SARS-CoV-2 by either quantitative polymerase chain reaction testing (at SU) or reverse transcriptase polymerase chain reaction (at UCSF), with the first positive test date occurring between March 1, 2020, and June 30, 2020. The date of first positive test date was defined as the index date. Patients with localized skin cancers were excluded; age was not an exclusion criterion. Both sites obtained institutional review board approval, and deidentified patient data were shared in aggregate between institutions in a Health Insurance Portability and Accountability Act–compliant manner.

Definition of Baseline Characteristics

Demographic data included age at index date, race, ethnicity, and sex. Cancer-related data included cancer type, stage (per American Joint Committee on Cancer Staging System 8th Edition), and most recent cancer treatment or diagnostic procedure. Active cancer was defined as cancer detectable on the most recent imaging study or laboratory test within 1 year prior to the index date and included patients receiving adjuvant therapy. Active management was defined as the receipt of cancer-directed therapy or the diagnostic procedure within 2 months prior to the index date.

Changes in Cancer Management

For all patients, including those without active cancer, cancer management changes due to COVID-19 occurring after the index date were determined from documentation in the electronic medical record. Delays were calculated starting from the planned date of the next therapy or procedure to the actual date that therapy or procedure was given. We collected information on the nature of management that was changed (diagnostic procedure, surgery, radiation therapy, and systemic therapy), route of systemic therapy (intravenous [IV], or intramuscular [IM], or orally

[PO]), intent of treatment (palliative v curative), reason for change (clinical, ie, due to COVID-19 illness, v nonclinical), and duration of delay (measured from the date of the first anticipated dose or procedure that was foregone to date of resumption). For diagnostic procedure changes, intent of treatment was based on most aggressive therapy reasonable for the stage of disease at index date.

COVID-19–Related Outcomes

For all patients, we determined reason for COVID-19 testing (screening v not) and whether the patient was hospitalized due to COVID-19, need for critical care, length of stay, complications from COVID-19, and death.

Statistical Methods

Clinical and demographic characteristics were summarized in contingency tables. To illustrate the context of potential delays in cancer management, an alluvial diagram was created for all patients. The diagram included whether a change in cancer management occurred, nature of management, time of initial COVID-19 diagnosis, and intent of treatment. Time of initial diagnosis was dichotomized as either March 1 to April 30 or May 1 to June 30. The rationale for this cutoff is that relaxation of suspended clinical procedures at both Stanford and UCSF started in mid-April and continued into early May. For example, at elective procedures, surgeries resumed on April 21 at both Stanford and UCSF; elective radiology resumed on April 21 at Stanford and on May 4 at UCSF.

Odds ratio and their CIs were computed using Baptista-Pike in prism, and a χ^2 test was used to compute the significance of the difference in odds. Among patients who experienced a delay in cancer management, we compared the incidence of delay between subgroups (date of COVID-19 diagnosis, nature of management, intent of treatment, and reason for delay) using the χ^2 test. We also calculated median and interquartile ranges for the duration of delay and compared medians between the same subgroups using the Wilcoxon rank-sum test. Individual durations of delay were illustrated using a swimmer plot, stratified by the reason for delay. $P < .05$ was considered significant for statistical testing. No multiple testing adjustments were performed given the small sample size. Analyses were performed using statistical software R or Prism 8.

RESULTS

Patient Characteristics and Outcomes

Baseline characteristics at the time of diagnosis are given in the Data Supplement (online only). Between March 1 and June 30, 2020, a total of 131 patients with a cancer diagnosis tested positive for SARS-CoV-2 at Stanford and UCSF (Data Supplement). The mean age at presentation was 60 (range, 3-97) years. Sex was evenly split: 68 (52%) male and 63 (48%) female. A range of ethnicities were represented, including non-Hispanic White (60 patients,

46%), Hispanic (39 patients, 30%), African American (5 patients, 4%), and Asian (20 patients, 15%).

A diverse mix of cancer types were seen, with the most common being solid malignancies: breast (24 patients, 18%), GI (21 patients, 16%), and genitourinary (10 patients, 15%) cancers. Twenty-nine patients (22%) had hematologic malignancies. Sixty-nine (53%) had active cancer and 50 (38%) received anticancer treatment (intravenous or oral therapy) in the last 2 months. Forty-one patients (31%) had been diagnosed with stage I cancer at the time of cancer diagnosis, and 28 (21%) had metastatic (stage IV) disease. Staging information was not applicable or unknown for 35 patients (27%). Patient outcomes related to COVID-19 illness are described in the Data Supplement. Fifty patients (38%) required hospitalization related to COVID-19. Of the 50 hospitalized patients, 19 (15%) required ICU care and 9 (7%) died of complications of COVID-19. Of the nine patients who died, 4 (44%) were undergoing active cancer treatment at the time of COVID-19 diagnosis.

Implications of COVID Infection on Cancer Management

Infection from COVID-19 affected cancer management for the majority of patients with active cancer. Of the 69 patients with active cancer, 55 (78%) patients were undergoing active cancer management in the 2 months preceding the COVID-19 diagnosis. Of the 55 patients undergoing active cancer management, 35 (64%) experienced a change in their cancer management plan. All these changes represented a delay in management, with one patient also experiencing a switch from IV to PO chemotherapy during chemotherapy delay as a result of the progression of disease. An additional three patients who were not undergoing active cancer management, but were either newly diagnosed with cancer or developed recurrent cancer, experienced a delay in cancer management. Among the 38 patients who had a delay in cancer management, most were diagnosed with COVID-19 in March to April (25 of 38, 66%). The most common management was IV or IM systemic therapy (19 of 38, 50%). The intent of treatment was palliative for the majority of patients (24 of 38, 63%) (Table 1). The patients who were receiving palliative intent therapy all had metastatic or incurable relapsed or refractory disease (in the case of a solid tumor primary) or hematologic malignancy. In total, two patients with hematologic malignancies had potentially curable disease with allogeneic hematopoietic stem-cell transplantation but were undergoing palliative intent chemotherapy due to age and/or disease status. The most common reason for delay in management or treatment was not guided by clinical factors (74%, Table 1). Clinical factors included concerns about the individual patient's status: for example, the need to recover from a recent hospitalization or desire for the resolution of illness before administering potentially myelosuppressive therapy, even among minimally symptomatic patients. In all cases, these

clinical reasons were due to COVID diagnosis or related complications. Nonclinical reasons were all related to the requirement for a repeat negative COVID-19 test, resolution of symptoms, and/or clearance from an infectious disease specialist prior to starting or resuming treatment or undergoing a procedure. Nonclinical reasons were therefore all due to institutional guidelines, which required documented COVID-19 clearance prior to entry to patient care areas. There was no difference in the incidence of delay among any of these subgroups (Table 1).

The alluvial plot illustrates the incidence of delay based on the intent of treatment and timing of COVID-19 diagnosis (Fig 1A) and highlights the fact that a disproportionately greater number of patients who were diagnosed with COVID-19 in March to April experienced a delay in receiving palliative treatment. This prompted a post hoc investigation into factors correlated with management changes. As shown in Figure 1B, there was no significant difference in the incidence of a delay in management based on the timing of COVID diagnosis or treatment intent alone; however, for patients on palliative intent therapy, there were more delays among those diagnosed with COVID-19 earlier (March/April) rather than later (May/June) (OR, 4.2; 95% CI, 1.03 to 17.3; $P = .0497$) (Fig 1B). This association was not found among patients undergoing curative intent treatment (OR, 0.89; 95% CI, 0.13 to 5.58; $P = .91$). There were no significant differences in the incidence of delays in management when comparing institution or routes of administration of systemic therapies. In addition, we did not find any significant differences in the occurrence or duration of delays in management based on race or ethnicity, that is, White versus non-White and Hispanic versus non-Hispanic. This analysis was not done for Black/African American versus non-Black/African American given the low frequency of the former.

Duration of Delays in Management due to COVID Infection

Overall, the median duration of delays in cancer management was 21 days with a range of 5-112 days (Table 1). There was no statistically significant difference in the duration of delay based on predefined subgroups (Table 1). A swimmer plot of individual durations of delay, categorized by reason for delay, can be found in Figure 2 (clinical reason, median duration 22 days; nonclinical reason, median duration 21 days). Of note, three patients were diagnosed with new or recurrent cancer at the index date; the date of first anticipated dose or procedure was estimated based on what could be reasonably expected with normal, pre-COVID-19 practices.

In this retrospective cohort study of two institutions, we found that patients diagnosed with cancer and COVID-19 were likely to experience a delay in cancer-directed management. No differences in the incidence or duration of delay were found based on the timing of COVID-19 diagnosis, type of management, intent of treatment, or reason for delay.

TABLE 1. Incidence and Duration of Delays in Cancer-Directed Management Due to COVID-19 Illness

Characteristic	Active Cancer Management Prior to COVID-19 Diagnosis ^a (N = 55)	Incidence of Delay in Management (N = 38) ^b	Duration of Delay in Management ^{a,c} Median Days (IQR)
Date of COVID-19 diagnosis			
March-April	33 (60%)	25 (66%)	21 (17-30)
May-June	22 (40%)	13 (34%)	21 (14-29)
Management type			
IV or IM therapy	28 (51%)	19 (50%)	21 (21-42)
PO therapy	18 (33%)	11 (29%)	16 (10-28)
Radiation therapy or surgery	5 (9%)	4 (11%)	21 (19-26)
Diagnostic procedure	4 (7%)	4 (11%)	16 (14-27)
Intent of management			
Curative	19 (35%)	14 (37%)	21 (17-29)
Palliative	36 (65%)	24 (63%)	21 (15-33)
Reason for delay in management			
Clinical	—	10 (26%)	22 (9-46)
Nonclinical	—	28 (74%)	21 (17-28)

^aNo statistically significant differences between subgroups.

^bThree patients did not have active cancer at the time of COVID-19 diagnosis. They were either newly diagnosed or developed recurrent cancer.

^cOnly applicable to patients with a change in management.

However, a post hoc analysis suggested that among patients undergoing palliative therapies, those who were diagnosed with COVID-19 early in the pandemic had more frequent delays than those diagnosed later. These findings illustrate the effects of COVID-19 diagnosis and related policy changes on the receipt of timely cancer care.

The majority of patients (64%) undergoing active cancer management who were diagnosed with COVID-19 experienced a delay or modification in care at both institutions. There were multiple reasons for delays, including reasons not directly related to the patient's clinical care, such as the need for documentation of COVID-19 clearance prior to being admitted to any clinical site. Such policies and provider decisions led to an overall median duration of a delay of 21 days, with a wide range (13-69 days). Such delays are nontrivial in the care of patients with cancer.²⁵⁻²⁷ In some cases, the delay was prolonged because of persistent positive tests or difficulty scheduling testing. These barriers to testing may have been exacerbated by variable turnaround times in COVID-19 testing. In California and other regions of the country, delays in testing turnaround for various reasons have led to a recent spike in time from specimen collection to test the result of up to 14 days that vary by testing location.²⁸ These testing issues may differentially affect certain populations such as those living in rural areas,²⁹ possibly exacerbating known disparities. The need for broadly accessible and rapid, yet specific testing is further highlighted by the findings presented here.

Among the possible reasons for delaying treatment was the concern that immunosuppressive systemic therapy could also worsen the course of the infectious illness or lead to complications. We found that therapy had a tendency to be delayed less frequently later in the course of the pandemic, when oncologists had gained some experience and may have had access to more data on the risks of cancer treatments in COVID-19–positive patients, especially for those treated with palliative intent.^{4,5} This highlights the continued need for large collaborative efforts, such as the COVID-19 and Cancer Consortium,^{4,8} TERA-VOLT,³⁰ National Cancer Institute COVID-19 in Cancer Patients Study,³¹ and ASCO's Survey on COVID-19 in Oncology,³² that will contribute to making available a more precise identification of factors to assist patients and their oncologists to make informed decisions about plans of care.

Our findings are limited to the San Francisco Bay Area, where local COVID prevalence was relatively controlled. As of August 2020, there has not yet been a surge of COVID-19 cases that overwhelmed the available healthcare delivery systems. This was not necessarily what was expected in March 2020, at the very beginning of the national COVID-19 epidemic. This uncertainty, as well as examples of dire shortages of personnel and resources in the Northeast of the United States,⁶ likely influenced many of the decisions made by local healthcare professionals and administrators that are highlighted in this study. Although COVID-19 is a

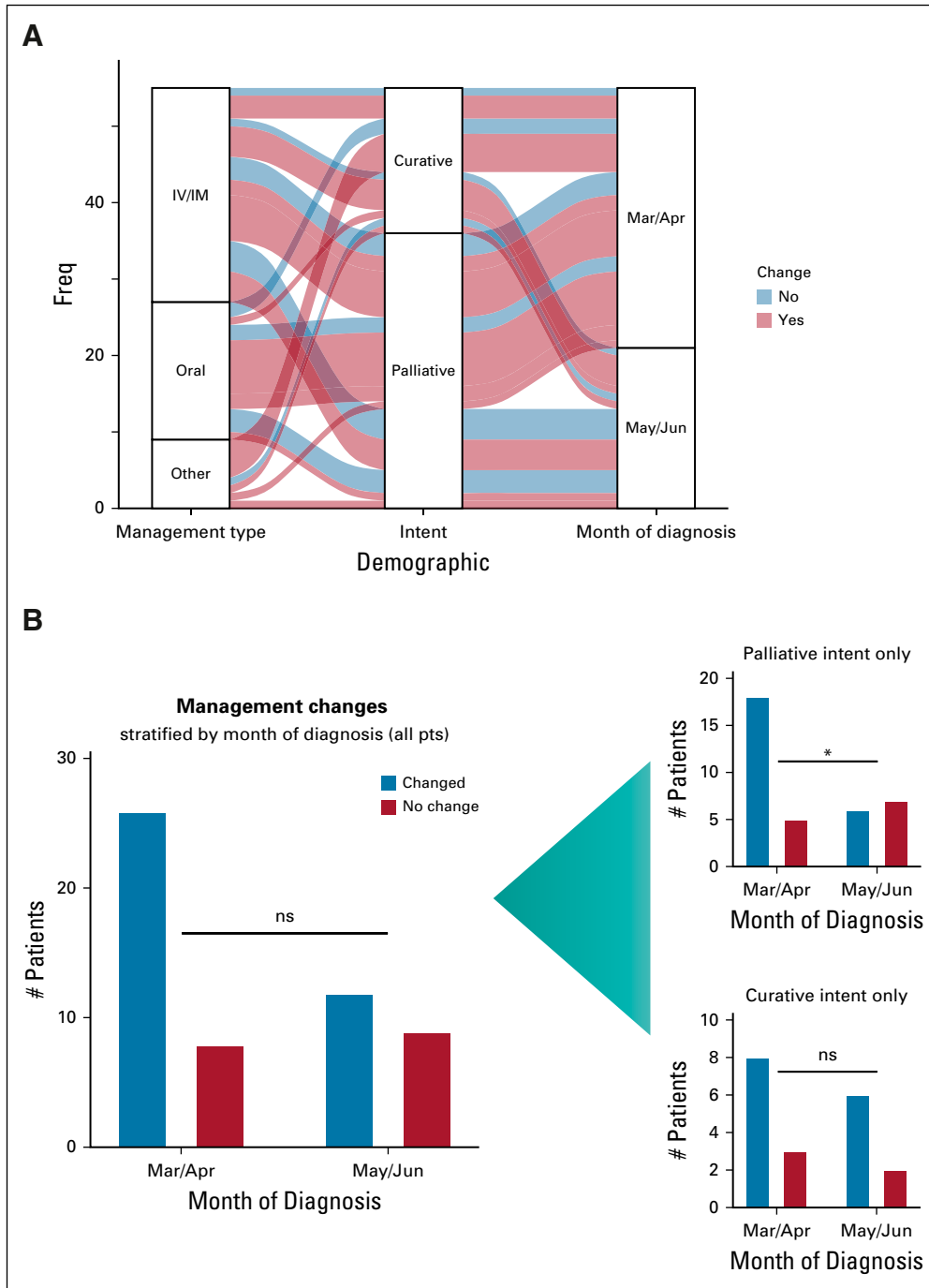


FIG 1. Abbreviations: pts, patients. (A) Alluvial plot of management changes stratified by treatment type, intent of treatment, and month of COVID-19 diagnosis. IV or IM: intravenous or intramuscular systemic therapy, oral: oral systemic therapy, other: surgery, radiation, or diagnostic procedure. (B) Bar graphs of management changes, divided by the month of diagnosis and separated by treatment intent. *indicates $P < .05$.

global problem, we have learned that care delivery is variable and highly dependent on local and regional factors.³³⁻³⁵ For those with overwhelmed healthcare systems, reduced resources may be an issue.³⁵ Patient fear of

exposure through the healthcare system may also play a role.³⁶ Further studies from diverse geographic regions may provide additional insight into how the location affects local policies and informs treatment decisions.

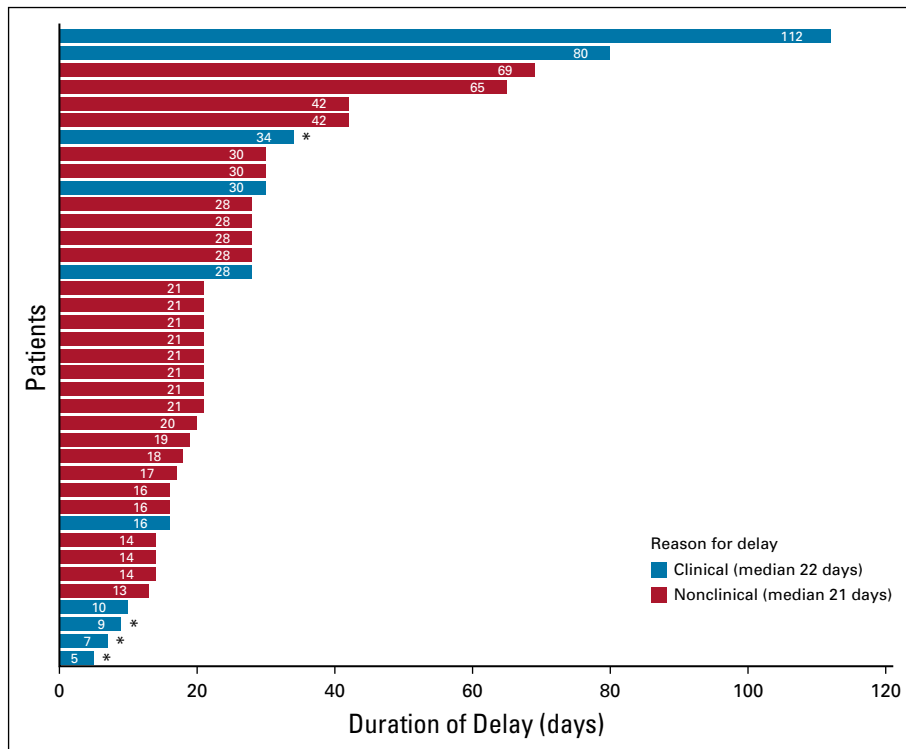


FIG 2. Swimmer plot of the duration of delay in cancer-directed management due to COVID-19 illness among patients with cancer. Bars are color coded by reason for delay, orange representing a clinical reason and blue representing a nonclinical reason. *indicates patient death.

Larger cohort studies are needed to validate and extend our findings. Our study is retrospective and limited by sample size. In addition, medical record review is not entirely sensitive in identifying delays in cancer care, as some may not be documented. The occurrence of delays may therefore be higher than reported. Some of the observed trends, such as differences in management depending on the route of administration of the intended treatment, would benefit from a larger sample size to draw more definitive conclusions. The inclusion of patients from two neighboring academic centers may limit external validity; however, it highlights local trends. Finally, it will take time to fully appreciate the impact COVID-19 has had on cancer outcomes. Although we identified a delay for a significant majority of patients, we

are unable to comment on its impact, if any, on clinical outcomes.

COVID-19 has changed many aspects of cancer care delivery, and the full, lasting impact of these changes remains largely unknown. Our study represents an early effort to quantify management changes due to COVID-19 in affected patients and further characterize the factors that lead to management changes in a real-world population. Institutional policies, such as the need for documentation of COVID-19 clearance prior to being allowed to enter a clinical facility, may contribute to management delays and may ultimately affect patient outcomes. Further collaborative studies will help us understand the full impact of local and regional policies on many dimensions of patient care that meaningfully contribute to health outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Changes in Cancer Management due to COVID-19 Illness in Patients With Cancer in Northern California

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