Received: 10 April 2020 | Accepted: 13 April 2020

DOI: 10.1002/hed.26196

SPECIAL ISSUE

WILEY

Should we wait or not? The preferable option for patients with stage IV oral cancer in COVID-19 pandemic

Atanu Bhattacharjee PhD[1] | Vijay M. Patil MD[2] | Rajesh Dikshit PhD[1] | Kumar Prabhash MD[2] | Arjun Singh MDS, MFDS[3] | Pankaj Chaturvedi MS, FACS[3]

[1]Section of Biostatistics, Centre for Cancer Epidemiology, Tata Memorial Centre and HBNI, Mumbai, India

[2]Department of Medical Oncology, Tata Memorial Centre and HBNI, Mumbai, India

[3]Department of Head and Neck Oncology, Tata Memorial Centre and HBNI, Mumbai, India

Correspondence
Pankaj Chaturvedi, Department of Head and Neck Oncology, Tata Memorial Centre and HBNI, Mumbai, India.
Email: chaturvedi.pankaj@gmail.com

Abstract

Background: The coronavirus infection is rapidly spreading, putting a strain on health care services across the globe. Patients with oral cancer are susceptible often immunosuppressed due to the disease and/or the treatment received.

Methods: We performed a simulation of the currently available data using a multistate and hazards model to provide an objective model for counseling and decision making for health care workers.

Results: Stage IV patients with oral cancer who did not receive treatment had progression of disease and an increased mortality rate compared to patients who receive treatment but did not contract COVID-19. The patients who received treatment and got affected with COVID-19 had a far worse impact and higher mortality rate than all other groups.

Conclusion: Isolation and deferring treatment for stage IV patients with oral cancer, so as to avoid hospital visits and contraction of COVID-19, is an advisable strategy based on this model.

KEYWORDS

cancer, coronavirus, COVID-19, simulation

1 | INTRODUCTION

As of the beginning of April, over a million people across the globe have been tested positive for the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] Having begun in Wuhan, China, the epicenter of this pandemic has shifted to the United States over the past 3 months. Parallel large-scale outbreaks have occurred in Italy and Spain with a majority of countries struggling to contain its spread. Patients with cancer are believed to be one of the most vulnerable populations due to the immune compromised state caused by both the disease and its treatment.[2]

India has one of the largest incidences of oral cancer in the world. With the mounting evidence on COVID-19, there are no systematic reports of patients with cancer with COVID-19, let alone oral cancer. Patients with these cancers are more likely to succumb to COVID-19 than the cancer itself. It is believed that the SARS-COV-2 would accelerate cell death in a relatively short span of time, especially in patients receiving chemotherapeutic agents where the underlying immunity level is substantially low. Most health care administrators are deferring early stage diseases to be attended to after the situation subsides. The biggest brunt is being borne by the advanced stage patients with oral cancer, especially stage IV. Almost all of these tumors will progress to an unresectable stage by the time the pandemic is contained. Hence planning of intervention and an adequate support strategy is required for the best service to be established.[3]

We present a simulation model using a multistate approach with transition-specific hazard functions that would predict the outcomes of stage IV patients with oral cancer who receive cancer-directed treatment and get infected with SARS-CoV-2 and the same patients if they do not receive any cancer-directed treatment and do not get infected with SARS-CoV-2 during the pandemic. This model will provide a unique approach for setting suitable strategies taking into account the current complex scenario of social distancing, human physiology, and heterogeneity of the patients' disease status.

2 | PATIENTS AND METHODS

The conventional infectious disease model considers an exponentially increase in cases during the transition period.[4] The ordinary differential equations are compatible to work with the exponential transition period model. The methodology of exponential time periods was done using the Gillespie algorithm.[5] Since the time gaps are based on the patient's disease status, we divided them into states based on the treatment received and infected with SARS-CoV-2 and no treatment received and not infected with SARS-CoV-2, so that a hazard model could be applied.[6] Model structures were applied through agent-based stochastic procedure.[7]

We assumed that patients with progressive disease and those receiving active treatment could not avoid a hospital visit and would continue rendering further treatment. Any of the above treatments would decline their immunity level from 0% to 100%. Due to social distancing and stringent mobility criteria, we assumed that there were no follow-up visits and these patients would have a nil to minimal risk of contracting COVID-19. The states are expressed as E^1, E^2, E^3, and E^4 depicted in a directed acyclic graph (DAG).[8] The corresponding time shift from one state to another is defined by time T^1, T^2, T^3, and T^4, respectively (Figure 1).

A multistate model was used to specify the treatment initiation, disease progression, COVID-19 transmission and death. A cohort of stage IV patients with oral cancer being treated or not was considered for analysis and their data were simulated. The transmission time was generated assuming that the transmission would occur during their hospital visit. The transmission probabilities and cumulative incidence were generated. The computation was performed using R software. The "mstate" and "muhaz" packages were used.

2.1 | Multistate model

Multistate models are often used to describe the life history of an individual. It defines several possible events for a single individual or the dependence between several individuals. Events are considered when there is a transition between the states. This model is useful to represent an extremely flexible approach that can model almost any kind of longitudinal failure time data.[9] Our model was formulated with states and transition steps. The DAG is formulated to describe the transition and time period for the transmission (Figure 2).

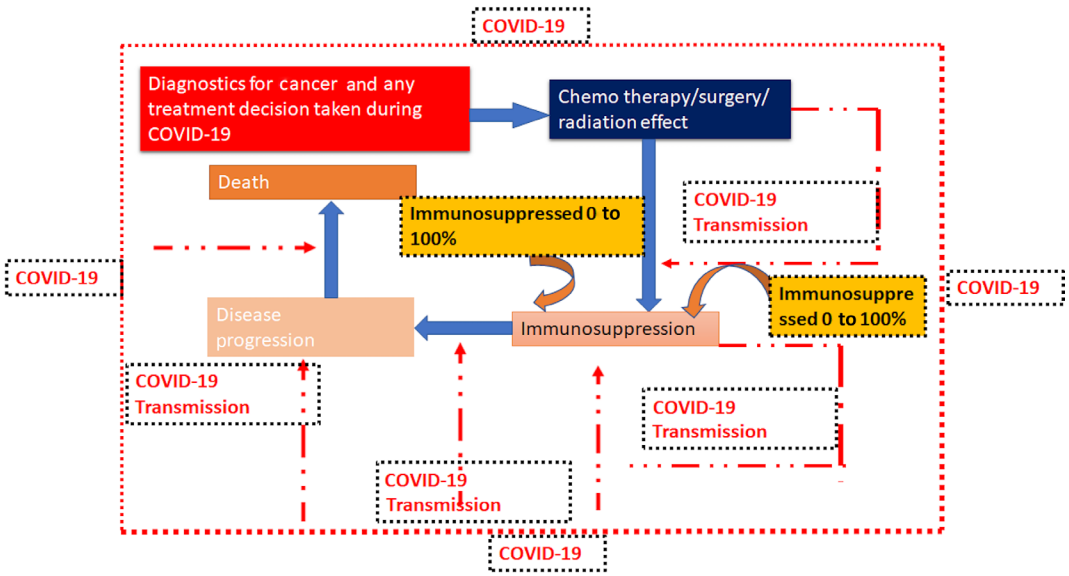

FIGURE 1 Overview of COVID-19 transmission among stage IV patients with oral cancer [Color figure can be viewed at wileyonlinelibrary.com]

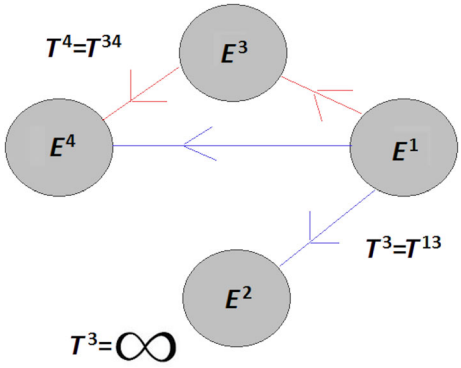

FIGURE 2 Multistate model transmission of COVID-19 among stage IV patients with oral cancer [Color figure can be viewed at wileyonlinelibrary.com]

Patients who continue receiving treatment were defined as E_i, and there could be n number of patients theoretically. Another state that received no treatment is defined as E_j. Here, E_1, E_2, E_3, E_4 shows the transition from states E_i to E_j while $i < j$. We used the stochastic process defined as $(X_{(t)})$, $t \geq 0$ to explain the different states. The superset of states was defined as $\varepsilon = \{E_1, ..., E_n\} \cdot S_i = \inf\{t \geq 0 | X_t = E_i\}$.

We then formulated the transition times of state E_j from E_i as $T_j = S_j - S_{\max\{k|k<j, S_k<\infty\}}$, assuming that $S_0 = 0$. The entire process was then defined by the transition time T_j to state E_j. The hazard functions h_{ij} for the transition from i to j was defined as $T_{ij} \sim F_{ij} = 1 - \exp\left\{-\int_0^t h_{ij}(u)\,du\right\}$ and $T_j = \min_{i\in\{1,...,J-1|T_i<\infty\}} T_{ij}$. The cumulative distribution was presented as F_{ij} for the transition from E_i to E_j. Finally, all hazards were considered as constant X using the Markovian structure.

2.2 | Hazards model

Assuming that the primary setups of the patients are presented with state E_1, further two states would be formulated as E_2 and E_3. The intermidiate and absorbing state would be defined as E_4.

The probability of transition from E_i at time s to state E_j at time t is presented as $p(s, t) = P[X = E_j | X_s = E_i]$ for $s \leq t$.

If $i < j$ and $\neq j$, it may be formulated as $p_{ii}(s,t) = \exp\left\{-\int_{s-S_i}^{t-S_i} h_{i4}(u)du\right\}$. Transition from $i = 4$ to $i = 4$ was not possible, but $i = 1$ to $j = 2, 3, 4$ were possible choices. Similarly, $i = 2$ to $j = 3, 4$ were the other possibilities, that is, $p_{i4}(s,t) = 1 - \exp\left\{-\int_{s-S_i}^{t-S_i} h_{i4}(u)du\right\}$ and $p_{ii}(s, t) = 0$.

Assuming that S_1=0, the transition probability can be obtained through integration

$$p_{11}(s,t) = \exp\left\{-\int_s^t h_{12}(u)\,du - \int_s^t h_{13}(u)\,du - \int_s^t h_{14}(u)\,du\right\},$$

$$p_{12}(s,t) = \int_s^t p_{11}(s,u) h_{12}(u) p_{22}(u,t)\,du,$$

$$p_{13}(s,t) = \int_s^t p_{11}(s,u) h_{13}(u) p_{23}(u,t)\,du,$$

$$p_{14}(s,t) = 1 - p_{11}(s,t) - p_{12}(s,t) - p_{13}(s,t).$$

This process was defined as X for state E_1 shifting from time s to u. The state E_2 or E_3 will move from time t. The transition probability p_{12} and p_{13} can be obtained by calculating the integration over u. This integration can be obtained by simulating the transition time linked to the probabilities (Figure 3).

2.3 | Simulation of hazards

We simulated the hazard function to understand the magnitude of mortality. The transition specific hazard function was formulated with the assumption that hazard with mean $\mu = 4$ will specify the constant function with $h(t) = (1/\mu)$ having parameter $\mu = 4$. The time points T_{ik} by the hazard functions can be explained in the DAG (Figure 2). The minimum time period for shifting one state to another state is represented as prefixed k. It was possible to take a minimum of k. If the transition time is T_j and connecting state E_j. Therefore, we can simulate X from the initial state T_{1k} to calculate the first transition within a minimum period. The simulation then could be obtained by the corresponding state E_j. It was iterated until it became nil at the end of the simulation.

The hazard function was formulated as $h(t)$ with piecewise constant function $h_{pc}(t)$. Using the msm package for simulation, the transition probabilities from the first state at time $t = 0$ by the process X was calculated.[10] We then simulated for N (Figure 4). Similarly, we used real data obtained from the website (https://ourworldindata.org/) and the data available on the coronavirus positive cases in India. These data are presented for the general population. The simulated portion for cancer patients' data is included for comparison[11,12] (Figure 4).

3 | RESULTS

Data simulated for patients with cancer are plotted in Figures 3 and 4. This model is prepared for an oncology hospital setup and simultaneously having the pressure to

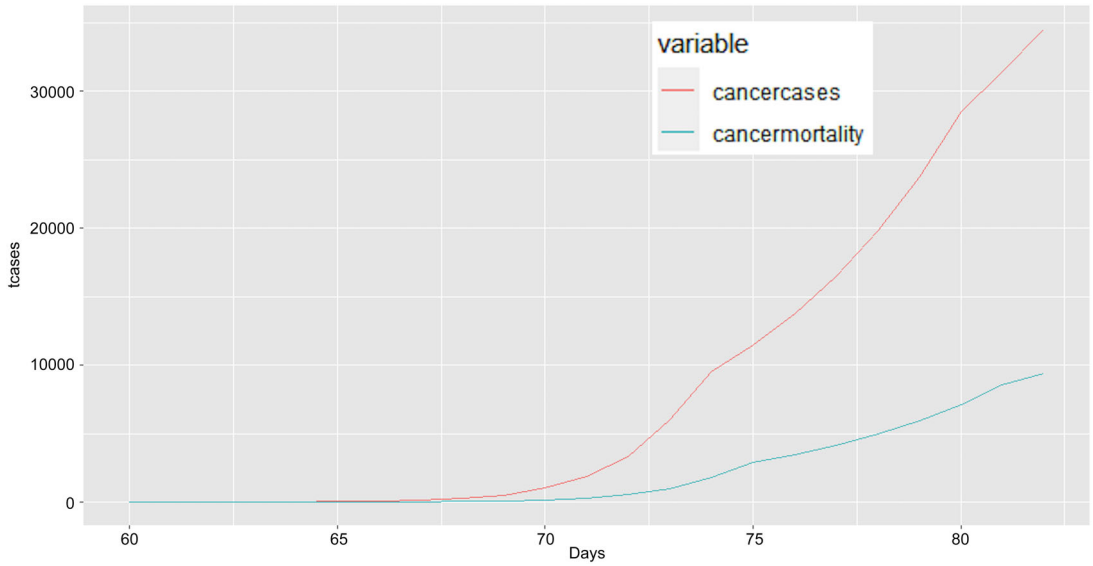

FIGURE 3 Projection of cancer cases and cancer mortality [Color figure can be viewed at wileyonlinelibrary.com]

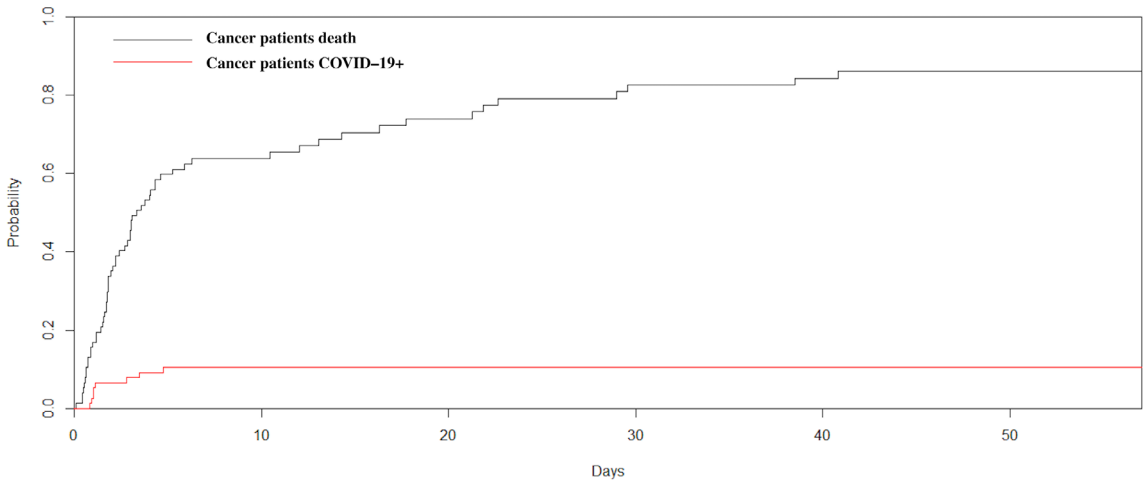

FIGURE 4 Comparison of patients with cancer infected by COVID-19 and patients with cancer [Color figure can be viewed at wileyonlinelibrary.com]

deal with COVID-19. The appearance of cancer cases is natural, and the cumulative number is presented by the red line in Figure 3. This is a noncommunicable disease that will report at its own pace, and the mortality rate without treatment will merge in Figure 3. But an alarming situation is present as the presence of COVID-19 is added. Probability of patients with cancer getting infected by SARS-CoV-2 for the next 60 days is plotted as a red line in Figure 4. Similarly, their probability of death is plotted as a black line in Figure 4.

Furthermore, we separated them into two groups, that is, group A and group B (Figure 5). Group A represents patients undergoing cancer-directed treatment during the pandemic, and group B was those that were restricted due to health services not rendering treatment. The 30-day mortality rate in our hospital audit was 0.9% after completion of the treatment.[13] However, there are no data to suggest the probability of death when no treatment is rendered to stage IV patients with oral cancer. We accumulated the number of patients who join the pool as untreated (group B). Even if we consider all these patients eventually die, the risk of death within the 60 days is lesser than those who contract SARS-CoV-2 and die. In absence of treatment, the disease will progress and increase mortality, but does not exceed the mortality of those infected with SARS-CoV-2. The simulated presentation on groups A and B demonstrated

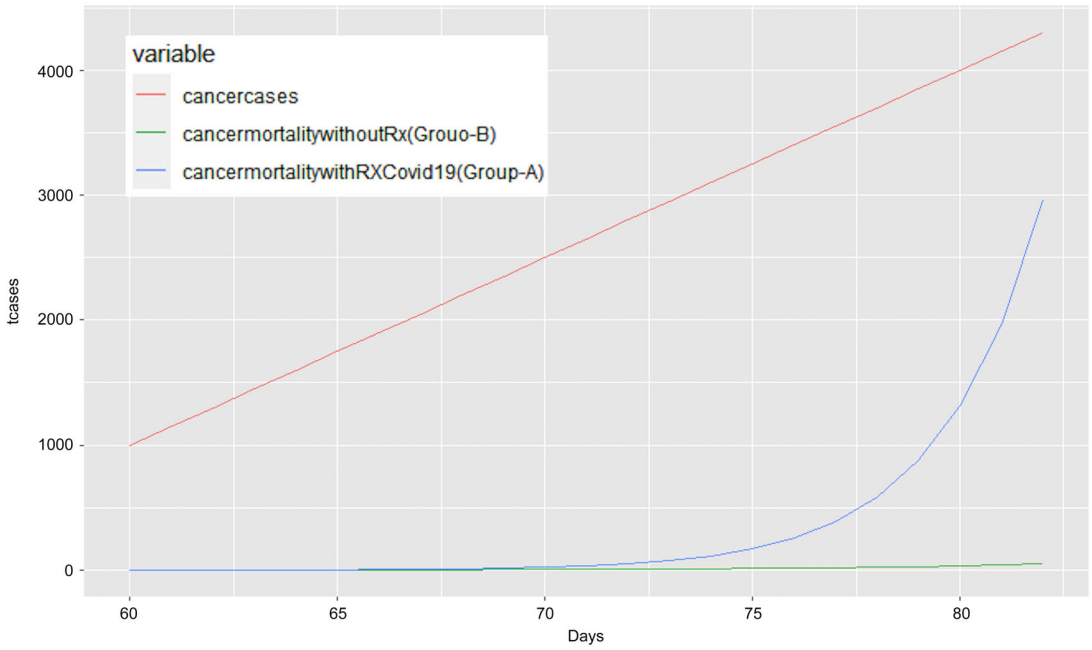

FIGURE 5 Comparison of patients receiving treatment and being infected by COVID-19 and patients not receiving cancer directed treatment [Color figure can be viewed at wileyonlinelibrary.com]

different scenarios. We should prefer to defer cancer treatment in these patients restricting the mortality to them.

The current patient load in our hospital is between 800 and 1000. Each day, 150 patients are registered on average. In the past 3 weeks, a total of 4150 should have been registered. The accumulated cancer mortality of patients not being treated (group B) will be inclined linearly and we can expect that it can come close to 50. We assumed that group B will see a cumulative increase of 10% in the rate of patients dying. In contrast, once infected by COVID-19, we expect to see a 50% cumulative increase in patients dying in group A. The solution could revolve around treating the patient with cancer efficiently with minimal clinical visits reducing their chance of infection.

4 | DISCUSSION

Countries across the world are implementing measures from national quarantines to school closures, to slow down the spread of the coronavirus. More than a third of humanity is under some form of restriction.[14] A few reports have described patients with cancer in quarantined cities struggling to obtain cancer-directed services and essential medication.[15] Over time, this will exacerbate due to interruptions in scheduled surgeries, chemotherapy, and radiotherapy in order to prioritize hospital space and care for the seriously ill COVID-19 patients.

Among the patients with cancer who develop COVID-19, treatment of the cancer will be delayed in order to prioritize treatment for the infection. Many physicians and surgeons around the world are being forced to take this tough call on an individual patient basis. With these limited resources and capacity, it is important to understand the implications it has on patients with cancer with and without COVID-19. Given the acute time frame of COVID-19 infection and lack of any retrograde data, a prospective study of scale cannot be accomplished. The challenge comes about when we need to triage cancer care during this pandemic. In our analysis, we assumed that patients treated for cancer will have a lesser risk of contracting the virus at the hospital due to the measures taken by the governments. At the same time, their chances of disease inflammation and death are relatively high due to the cancer or the treatment received.

The simulated work presented here is to visualize the impact of COVID-19 in the worst case scenario so as to support policy makers to make the hard decisions. Nonetheless, decisions on patients care are required to be taken as per the case, rather than abide by blanket guidelines. Due to the limitation of adequate real-world data and follow-up on COVID-19, we cannot provide personalized recommendations regarding cancer care. The increased mortality of patients seen in this model should caution oncologists. The risk-benefit ratio should be discussed with patients before administering any definitive treatment. We propose that forceful steps are required to reduce the frequency of hospital visits for patients having cancer during this time. Proper isolation techniques are required to mitigate the risk of transmission. Risk factors like disease

severity, recent chemotherapy received can increase the chance of illness and mortality due to COVID-19. It is also required to take steps to eliminate cross infection between the patients and health care workers.

With the situation gradually unfolding, there is not much we can do as health care providers but to adapt as best we can. In case of suspicion, appropriate isolation techniques need to be instated. Among patients with cancer, receiving recent chemotherapy does increase the risk of severe illness. This model helps us better understand the survival trajectory of patients with oral cancer who might be affected by COVID-19.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have made a significant contribution to this article from concept to implementation and publication.

ORCID

Arjun Singh https://orcid.org/0000-0002-8119-8439
Pankaj Chaturvedi https://orcid.org/0000-0002-3520-1342

REFERENCES

1. WHO. *Coronavirus Disease 2019 (COVID-19) Situation Report—73*. Geneva: World Health Organisation; 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200405-sitrep-76-covid-19.pdf?sfvrsn=6ecf0977_2
2. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41(2):145.
3. Yamanaka Y, Uchida K, Akashi M, et al. Mathematical modeling of septic shock based on clinical data. *Theor Biol Med Model*. 2019;16(1):5.
4. Anderson RM, Anderson B, May RM. *Infectious Diseases of Humans: Dynamics and Control*. New York, NY: Oxford University Press; 1992.
5. Gillespie DT. Exact stochastic simulation of coupled chemical reactions. *J Phys Chem*. 1977;81(25):2340-2361.
6. Lloyd AL. Realistic distributions of infectious periods in epidemic models: changing patterns of persistence and dynamics. *Theor Popul Biol*. 2001;60(1):59-71.
7. Estill J, Aubriere C, Egger M, et al. Viral load monitoring of antiretroviral therapy, cohort viral load and HIV transmission in Southern Africa: a mathematical modelling analysis. *AIDS (London, England)*. 2012;26(11):1403.
8. Pearl J. Causal inference in statistics: an overview. *Stat Surv*. 2009;3:96-146.
9. Hougaard P. Multi-state models: a review. *Lifetime Data Anal*. 1999;5(3):239-264.
10. Jackson CH. Multi-state models for panel data: the msm package for R. *J Stat Softw*. 2011;38(8):1-29.
11. Our World in Data [Internet]. https://ourworldindata.org/. Accessed April 10, 2020.
12. #IndiaFightsCorona COVID-19 [Internet]. MyGov.in; 2020 https://mygov.in/covid-19/. Accessed April 10, 2020.
13. Nair D, Singhvi H, Mair M, et al. Outcomes of surgically treated oral cancer patients at a tertiary cancer center in India. *Indian J Cancer*. 2017;54(4):616-620.
14. CDC. *Coronavirus Disease 2019 (COVID-19) in the U.S. [Internet]*. Atlanta, GA: Centers for Disease Control and Prevention. 2020 https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed March 31, 2020.
15. Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group. *Oncologist*. 2020:1-10. https://doi.org/10.1634/theoncologist.2020-0213.

How to cite this article: Bhattacharjee A, Patil VM, Dikshit R, Prabhash K, Singh A, Chaturvedi P. Should we wait or not? The preferable option for patients with stage IV oral cancer in COVID-19 pandemic. *Head & Neck*. 2020;42:1173–1178. https://doi.org/10.1002/hed.26196