JAP&T
TPA-Timişoara

Available online at http://journal-of-agroalimentary.ro

Journal of Agroalimentary Processes and Technologies 2023, *29*(1), 34-41

Journal of Agroalimentary Processes and Technologies

Oral Cancer During COVID-19 Pandemic and Non-Pandemic Periods: a Comprehensive Review

Roxana Buzatu[1], Ștefania Dinu[1], Alina Anton[2,3]*, and Mircea Rivis[4]

[1]Department of Dental Aesthetics, Faculty of Dental Medicine, "Victor Babeș" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Sq. No. 2, 300041 Timișoara, Romania
[2]Faculty of Pharmacy, "Victor Babeș" University of Medicine and Pharmacy Timișoara, Eftimie Murgu Square, No.2, 300041, Timișoara, Romania
[3]Research Centre for Pharmaco-Toxicological Evaluations, Faculty of Pharmacy, "Victor Babeș" University of Medicine and Pharmacy Timișoara, Eftimie Murgu Square, 300041, No. 2, Timișoara, Romania
[4]Faculty of Dental Medicine, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square No. 2, 300041 Timisoara, Romania

Abstract

Cancer is the devastating disease of our days, which requires increased attention, with continuous studies, to identify the most appropriate resolving solutions. Oral cancer is the most frequently encountered form of head and neck cancer group. The pandemic period was a real challenge for medical systems around the world, and the management of this situation was modified by the viral wave and by restrictions imposed all around the world. The first observed change was the intensification of telemedicine, the sorting of patients, in order to reduce as much as possible the visits to the hospital, and last but not least, changes were observed in the treatment schemes of the patients. The purpose of this paper is to analyze the changes observed both in the management of oral cancer and in the treatment schemes administered during the pandemic versus the non-pandemic period.

Keywords: oral cancer, pandemic, COVID-19

1.Introduction

Oral cancer (OC), also known as mouth cancer or oral cavity cancer, is a type of cancer that develops in the tissues of the mouth or throat. It can affect various areas, including the lips, tongue, cheeks, gums, mouth roof, and mouth floor [1]. OC is a common type of cancer worldwide, being the most encountered form of the head and neck group of cancers. According to the GLOBOCAN database, there were approximately 354,864 new cases and 177,384 deaths from lip and oral cavity cancer in 2020 [2]. The incidence of OC is higher in men than in women, and it tends to affect people over the age of 40, although younger individuals can also be affected [3]. The development of oral cancer is multifactorial, and several risk factors have been identified (Figure 1).

Disease control is indispensable in any period, regardless of the pandemic or non-pandemic situation. The term COVID started to be heard more and more frequently, starting in December 2019, when Wuhan, the city of Hubei Province of China was identified with a novel strain of the Coronavirus, with an impressive spreading capacity that was named by the World Health Organization (WHO) as the 2019 novel coronavirus (2019-nCoV). At the beginning of February 2020, the International Committee on Taxonomy of Viruses formally renamed the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the WHO formally named the illness produced by the Coronavirus Disease 2019 (COVID-19); an illness characterized by respiratory disorders, fatigue, fevers, coughs, muscle pain, and pneumonia [4]. Following the fast-increasing number of positive infected cases in China and slowly everywhere, on 30 January 2020, an international health emergency has been declared by the WHO because of the viral epidemic.

SARS-CoV-2 belongs to the *Betacoronavirus* genus, it is a single-stranded, enveloped, positive-sense RNA virus from the *Coronaviridae* family [5,6]. Governments worldwide implemented stringent measures to control its spread, including lockdowns, social distancing, and healthcare system

Corresponding authors: Alina Anton

prioritization. Consequently, non-essential medical services were interrupted, resulting in disruptions to OC diagnosis and management [4]. The pandemic severely impacted on OC screening programs due to the prioritization of resources for COVID-19 management [7]. Routine screenings, community outreach programs, and public awareness campaigns were suspended or reduced, leading to potential missed opportunities for early detection. During the pandemic, many patients hesitated or were unable to seek dental and medical care for fear of contracting the virus. This reluctance resulted in delayed OC diagnoses, with patients presenting at more advanced stages of the disease, compromising treatment outcomes and survival rates [8].

The aim of the present work is to summarize changes observed during and before/after the COVID-19 pandemic in OC management and treatment.

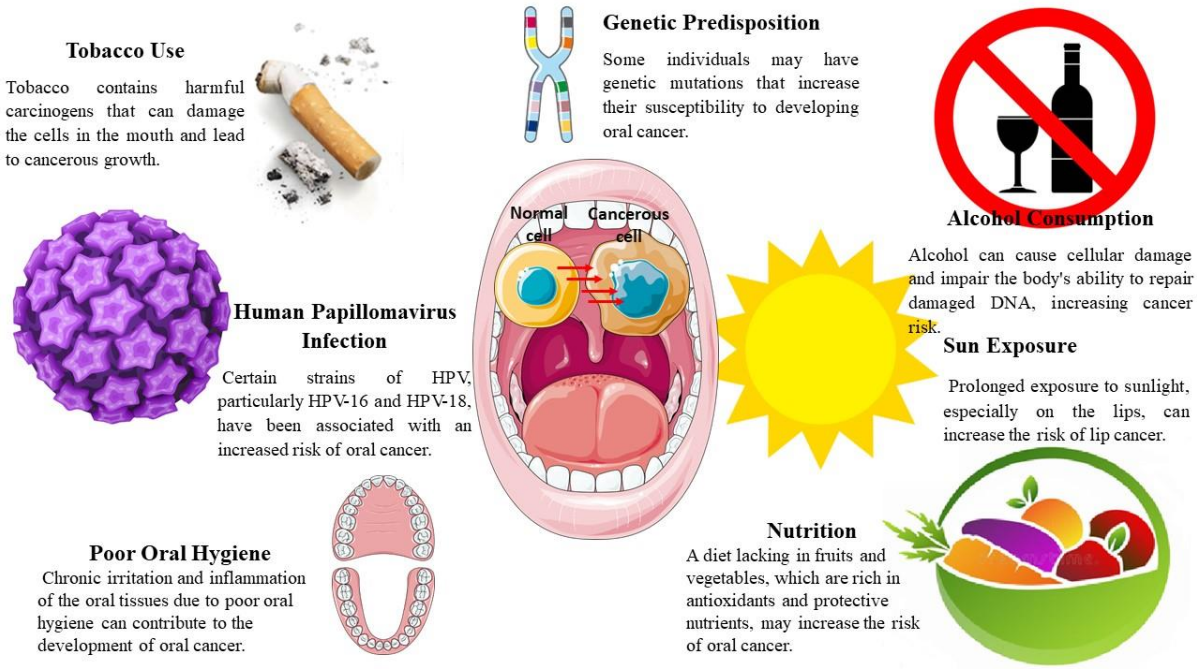

Figure 1. Main causes in case of oral cancer

2.Materials and method

Materials

PubMed, Scopus, and Web of Science databases were investigated to identify publications on the impact of COVID-19 in dentistry-related aspects, especially on OC, which had been published from the beginning of January 2020 to the end of July 2023. The terms used for the search of keywords were: oral cancer, COVID-19, SARS-CoV-2, COVID-19 transmission, COVID-19 dentistry, COVID-19 stomatology, SARS-CoV-2 contamination, COVID-19 prevention, and SARS-CoV-2 mechanism.

Method

The inclusion criteria applied for screening were papers written in English, which reported on oral cancer, SARS-CoV-2, and dentistry-related aspects of COVID-19 (Figure 3). The exclusion criteria applied were: papers in a language other than English; and studies not included in the three mentioned databases. Studies were first selected according to titles and abstracts; then studies that responded to the inclusion criteria were selected and their full texts were studied. The contents were analyzed, and results were extracted if the papers provided significant data regarding OC and COVID-19.

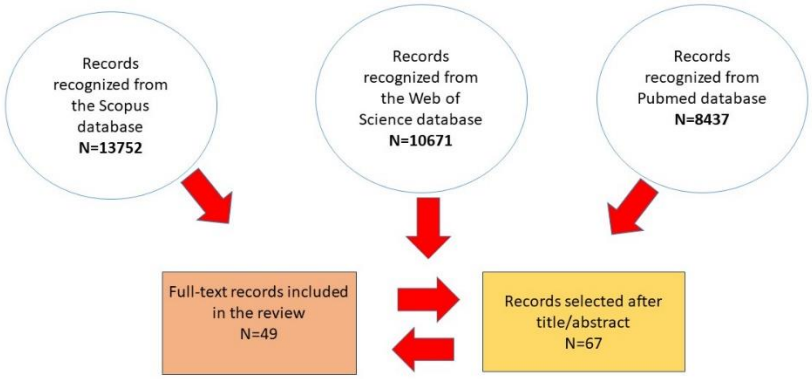

Figure 2. Systemic review flow chat

3.Results and discussions

An overview of the COVID-19 pandemic

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, emerged in late 2019 and quickly became a global health crisis. Tyrell and Bynoe isolated and cultivated firstly this family of viruses from patients suffering from common colds in 1965 [9]. Nucleocapsid proteins (N), spike glycoproteins (S), and membrane glycoproteins (M) determine viral virulence and functionality [10]. Acute Respiratory Distress Syndrome (ARDS) may result from the current SARS-CoV-2 outbreak, much like other zoonotic coronavirus outbreaks (SARS-CoV and MERS-CoV). The common chain of spread is by droplets that are shed when someone breathes, speaks, sneezes, or coughs. Patients over 80 years old were the target group with the highest mortality rate, and males predominated, representing 67% [11]. In the younger population (70–79 years), likewise, the male gender predominated, with a percentage of 77%. Patients under the age of 50 accounted for only 1% of COVID-19 deaths [12]. Most deceased SARS-CoV-2 patients presented several comorbidities, as follows: 48% had three or more comorbidities, 26% had two comorbidities, 23% had one comorbidity, and 1.2% without comorbidities. Cardiovascular diseases including hypertension and ischemic heart disease, and diabetes, are among the main preexisting pathologies [13].

Coronavirus virion proteins include a nucleocapsid, membrane, envelope, and spike glycoprotein (S). S glycoprotein mediates the adhesion and fusion to the host cell membrane. This crown-like appearance is caused by the S protein, which is assembled as a homotrimer and inserted into the membrane in multiple copies. Furin, a proprotein convertase, cleaves the S protein in virus-producing cells. In the mature virion, the S protein consists of two non-covalently associated subunits: S1 and S2. The S1 subunit binds the S2 subunit and ACE2 and attaches the S protein to the membrane. Infection occurs when S1 binds to the host receptor, and S2 fuses the host and viral membranes, releasing the virus' genome [14].

To date, it has registered more than 690 million infections around the world. The country with the most registered cases is the United States, with more than 100 million cases representing around 300,000/ 1 million people, followed by India, France, and Germany. The top 10 countries with the most cases of SARS-CoV-2 are presented in Figure 3 [15].

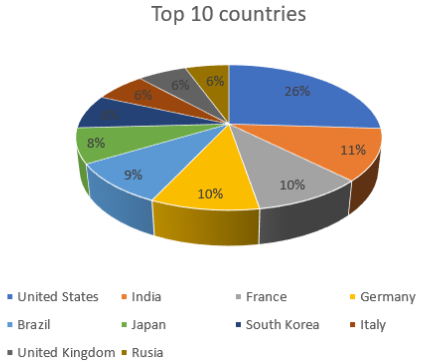

Figure 3. The top 10 countries in the world with the highest number of SARS-CoV-2 infections

Saliva samples have proven SARS-CoV-2 contamination, making a possible route of transmission for COVID-19. Because dental practitioners are always in close contact with patients and are likely to be exposed to saliva-contaminated droplets and aerosols generated during dental procedures, they are particularly vulnerable to infection with SARS-CoV-2. Surfaces

that are contaminated with saliva could also lead to multiple infections [16]. Due to their activation domain, the risk of cross-infection among oral healthcare workers and patients is high in oral healthcare settings. Because of this, helpful infection control protocols were needed. Hand hygiene is considered one of the most efficient measures to reduce the risk of transmitting microorganisms to patients [17]. Depending on the type of surface, the temperature, or the humidity of the environment, SARS-CoV-2 can persist for 7 hours or up to a few days [18]. This strengthens the requirement for rigorous hand hygiene and the significant importance of disinfection of all surfaces within the dental clinic. The use of protective equipment, gowns, gloves, masks (especially FFP2-masks authenticated by the European Union and N-95 masks validated by the National Institute for Occupational Safety and Health), and face shields or goggles, are required to protect skin and mucosa from possible infected fluids.

During the COVID-19 pandemic period, dentistry underwent a series of significant adjustments and changes. It was felt both on an emotional level by the patients and by the specialists in the field, but also on the level of a type of pathology and the number of patients. All these changes imposed modifications in health policies and guidelines. Thus, the changes made depended on the severity of the pandemic. These included limiting access to dental services for non-emergency patients at the peak of the COVID-19 pandemic and reducing the restrictions on non-elective dental care when control was taken over SARS-CoV-2. Besides the use of hand sanitizers, maintaining social distancing, and use of facemasks, it was imposed a maximal possible reduction of the amount of aerosol production in the dental setting, and monitoring the quality of air in the dental treatment spaces by limiting the use of air conditioners and ameliorating air exchange [19].

Changes in the management of oral cancer during the pandemic

Management of OC during the COVID-19 pandemic presents unique challenges due to the need to balance cancer treatment with infection control measures. The pandemic has disrupted healthcare systems globally, leading to modifications in cancer care protocols to minimize the risk of COVID-19 transmission while ensuring the best possible outcomes for patients with OC [20]. The main key aspects of managing oral cancer during the COVID-19 pandemic are presented in Figure 4.

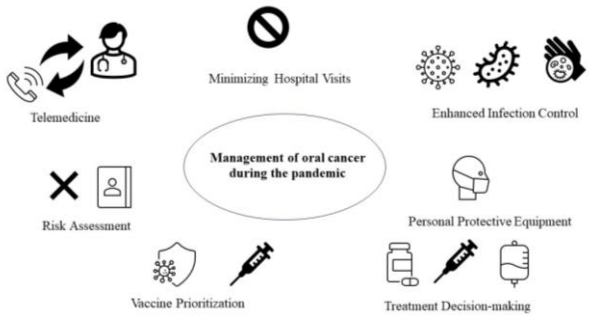

Figure 4. Changes in the management of oral cancer during COVID-19

Thus, to reduce the risk of exposure, healthcare providers may utilize telemedicine and virtual consultations for initial assessments, follow-up visits, and non-urgent discussions. Through these technologies, doctors can evaluate patients' conditions remotely and provide recommendations for further evaluations or treatments [21]. Another challenge for healthcare professionals is a thorough risk assessment that has to be done for each OC patient, to determine the urgency and appropriateness of treatment. Factors such as cancer stage, grade, and the patient's overall health condition should be considered in making decisions regarding treatment timelines. Treatment plans may need to be adjusted based on the risk/benefit analysis. For some patients, delaying elective surgeries or radiation therapy may be considered to minimize the risk of COVID-19 exposure [22]. However, for patients with advanced or aggressive OC, timely interventions may be essential to prevent disease progression. Patients receiving active treatment may be considered a priority group for COVID-19 vaccination. Vaccination can help protect vulnerable patients and reduce the severity of illness if infection occurs [23].

Appropriate protective equipment is critical for healthcare workers involved in the direct care of OC patients, to minimize the risk of infection transmission. Regular training and reinforcement of infection control protocols are necessary to ensure healthcare staff's safety. Healthcare facilities implemented rigorous infection control measures to minimize the risk of COVID-19 transmission among patients and staff. Regular sanitization of surfaces, enforcement of physical distancing, and screening for COVID-19 symptoms are some of the

measures that should be adopted [24]. To reduce the potential exposure to COVID-19, healthcare providers may implement strategies to minimize the number of hospital visits required for patients. This could include consolidating appointments and conducting multiple tests in a single visit whenever feasible.

Supportive care is another important measure to implement. During the pandemic, psychological and emotional support for oral cancer patients is crucial. Social isolation and anxiety related to COVID-19 may adversely impact patients' mental well-being, so healthcare teams should provide additional resources and support to address these concerns [25]. It is important to note that the management of oral cancer during the COVID-19 pandemic may vary depending on regional infection rates, healthcare infrastructure, and government guidelines. Patients should maintain open communication with their healthcare providers to receive the most appropriate and safe care during these challenging times.

Oral cancer treatment challenge during a pandemic

Treatment options for OC depend on various factors, including the stage of cancer, the location and size of the tumor, the overall health of the patient, and other individual considerations. The main treatment modalities for OC include surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, and palliative care [26]. Surgical treatment is the mainstay of therapies in incipient, but also in advanced stages of OC. Radiation therapy and brachytherapy have been used favorably as the first modality for treating patients with early stage, and they are the standard of care for patients with advanced OC stage as adjuvant therapy in postoperative cases. There is a trend for the use of a combination of chemotherapy with surgery and radiation therapy for patients with recurrent, advanced, and metastatic forms of cancer [27].

Although radiotherapy was considered the basic method, during the pandemic, things changed. Cancer patients are more likely to be old and have comorbidities. Different reports highlighted that COVID-19 is more aggressive in elderly and with comorbidities patients, thus reducing the frequency of hospital visits is warranted; a careful evaluation of the ratio benefit /risk for every patient should be performed; only non-deferrable and urgent cases should be safely planned for radiation; all the other treatments should be deferred. Radiation dose prescription, fractionation, and technique should be adapted to the emergency context. The decision 'less might be better' have to be taken into consideration during the pandemic scenario [28, 29].

Meantime, patients with cancer receiving chemotherapeutics need special attention because of their immunocompromised status which could possibly increase the risk of mortality [30, 31]. Another problem is nausea and vomiting symptoms, which are common for COVID-19 contamination and chemotherapy side effects. To differentiate it, the specialists need to consider the emetogenicity of therapeutical agents, and other risk factors including young age, female gender, and history of the symptoms with prior administrated cycles [32]. The most relevant neurotransmitters involved in COVID-19-induced nausea and vomiting are serotonin, cholecystokinin, and substance P, while in the case of chemotherapeutics, these are mainly mediated by dopamine, serotonin, cannabinoids, and substance P [32, 33]. Considering these, the management of nausea and vomiting in both cases includes the combination of a neurokinin inhibitor (e.g., aprepitant) and/ or a serotonin antagonist (e.g., ondansetron) [34]. Two studies from China have mentioned the augmented risk of mortality in patients with COVID-19 under chemotherapy [35, 36]. In addition, because of the downregulation of the immune system, patients who undergo chemotherapeutics are more susceptible to developing infections [37]. It was recommended that during the pandemic, these interventions have to be analyzed by considering the risks /benefits ratio of patients with cancer [38].

Immunotherapy drugs help boost the body's immune system to recognize and attack cancer cells more effectively. The possible side events and immune-related adverse effects of these therapies may potentially lead to more severities in patients with cancer and SARS-CoV-2 and increase mortality rates. Furthermore, the co-occurrence of pneumonitis during immunotherapy and COVID-19 may increase the possibility of death due to respiratory failures [39]. Other common side effects such as neutropenia and hypogammaglobulinemia during immunotherapy in patients with chronic lymphocytic leukemia can cause serious problems in patients with COVID-19 [40]. Thus, special attention to immunotherapy strategies must be paid, which could play more effective roles in patients

with both cancer and COVID-19. The programmed cell death-1/ programmed cell death -L1 blockade has been identified as a potential treatment solution to inhibit cytokine production and the activation of T cells in OC cells [41]. So far, four monoclonal antibodies have been approved for this blockade, including cemiplimab, nivolumab, toripalimab, and sintilimab [42]. A case report presented the situation of a woman with positive COVID-19 serological tests to whom it was administered cemiplimab and who presented digital ischemia [43]. Another report presented a case of a 25 years-old, Japanese man, who manifested acute encephalopathy 2 days after the second dose of the COVID-19 vaccine. He had been treated with nivolumab. He had an elevated fever and was confused upon admission, and the antibody test for anti-myelin oligodendrocyte glycoproteins was positive [44]. However, the causal relationship between viral effects and treatment is not completely elucidated.

Targeted therapy is a form of treatment that targets specific molecules or pathways involved in cancer growth and progression, leading to more focused and less harmful effects on healthy cells. Chimeric antigen receptor (CAR)-T cell therapy, one of the most important from this category, has obtained important results against hematological tumors by targeting cancer antigens [45]. To acquire CAR-T cells, T cells are separated from the patient's peripheral blood, then by genetic engineering technique, the cells are transduced to achieve the targeted recognition of the tumor., the autologous CAR-T cells, after cell amplification, are inserted back into the patients [46]. In reports, Atanackovic et al. [47] and Oh et al. [48] highlighted that T-cell immune responses following SARS-CoV-2 messenger RNA vaccination in patients with non-Hodgkin lymphoma receiving CAR T-cell therapy. Their findings suggest a potential security of immune protection against COVID-19 for patients whose treatment journey requires traveling by CD19 CAR T cells [49].

For advanced cases or those that are not responding to curative treatment, palliative care is provided to improve the patient's quality of life by managing symptoms and providing supportive care. Early detection is crucial for ameliorating the prognosis of oral cancer. Regular dental check-ups and self-examinations can help identify any unusual changes in the mouth, such as persistent sores, lumps, or patches, and seek timely medical attention.

The COVID-19 pandemic strained healthcare infrastructure worldwide, leading to overloaded hospitals and diminished healthcare resources. OC patients faced challenges in accessing timely and appropriate care, potentially compromising their prognosis. As the world navigates the post-pandemic era, prioritizing OC screening programs and ensuring adequate resources for timely diagnosis and treatment will be essential. Emphasizing the integration of telemedicine for follow-up care can aid in enhancing patient outcomes.

Conclusions

The COVID-19 pandemic has significantly affected OC, which is the most common form of head and neck cancer groups, with management and treatment being forced to face numerous challenges for patients and healthcare systems. To mitigate the long-term consequences, concerted efforts are needed to reinforce screening programs, improve patient education, and enhance healthcare infrastructure, thereby ensuring the effective management of oral cancer during and beyond the pandemic.

Compliance with Ethics Requirements. Authors declare that they respect the journal's ethics requirements. Authors declare that they have no conflict of interest and all procedures involving human or animal subjects (if exist) respect the specific regulation and standards.

References

1. Montero, P.H.; Patel, S.G., Cancer of the Oral Cavity, *Surg Oncol Clin N Am* **2015**, 24(3):491-508, doi:10.1016/j.soc.2015.03.006.
2. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, *CA Cancer J Clin* **2021**, 71(3):209-249, doi: 10.3322/caac.21660.
3. Lipsky, M.S.; Su, S.; Crespo, C.J.; Hung, M., Men and Oral Health: A Review of Sex and Gender Differences, *Am J Mens Health* **2021**, 15(3):15579883211016361, doi:10.1177/15579883211016361.
4. Fernandes, Q.; Inchakalody, V.P.; Merhi, M.; Mestiri, S.; Taib, N.; Moustafa, Abo El-Ella D.; Bedhiafi, T.; Raza, A.; Al-Zaidan, L.; Mohsen, M.O.; Yousuf Al-Nesf, M.A.; Hssain, A.A.; Yassine, H.M.; Bachmann, M.F.; Uddin, S.; Dermime, S., Emerging COVID-19 variants and their impact on SARS-CoV-2 diagnosis, therapeutics, and vaccines, *Ann Med* **2022,** 54(1):524-540, doi:10.1080/07853890.2022.2031274.

5. Chan, J.F.W.; Kok, K.H.; Zhu, Z.; Chu, H.; To, K.K.W.; Yuan, S.; Yuen, K.Y., Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan, *Emerg Microbes Infect* **2020**, 9(1):221-236, doi:10.1080/22221751.2020.1719902.
6. Lu, R.; Zhao, X.; Li, J.; Niu, P.; Yang, B.; Wu, H.; Wang, W.; Song, H.; Huang, B.; Zhu, N.; Bi, Y.; Ma, X.; Zhan, F.; Wang, L.; Hu, T.; Zhou, H.; Hu, Z.; Zhou, W.; Zhao, L.; Chen, J.; Meng, Y.; Wang, J.; Lin, Y.; Yuan, J.; Xie, Z.; Ma, J.; Liu, W.J.; Wang, D.; Xu, W.; Holmes, E.C.; Gao, G.F.; Wu, G.; Chen, W.; Shi, W.; Tan, W., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, *Lancet* **2020**, 395(10224):565-574, doi:10.1016/S0140-6736(20)30251-8.
7. Werner, M.T.; Carey, R.M.; Albergotti, W.G.; Lukens, J.N.; Brody, R.M., Impact of the COVID-19 Pandemic on the Management of Head and Neck Malignancies, *Otolaryngol - Head Neck Surg* **2020**, 62(6):816-817, doi:10.1177/0194599820921413.
8. Sandhu, P.; Grossman, S.; Beneng, K., The impact of the cessation of primary dental care services on oral cancer diagnosis at a single institution in the UK's epicenter during the COVID-19 pandemic, *Oral Surg* **2021**, 14(4):328-334, doi:10.1111/ors.12626.
9. Tyrrell, D.A.; Bynoe, M.L., Cultivation of viruses from a high proportion of patients with colds, *Lancet* **1966**, 1(7428):76-77, doi:10.1016/s0140-6736(66)92364-6.
10. Perlman, S., Another Decade, Another Coronavirus, *N Engl J Med* **2020**, 382(8):760-762, doi: 10.1056/nejme2001126.
11. Villani, F.A.; Aiuto, R.; Paglia, L.; Re, D., Covid-19 and dentistry: Prevention in dental practice, a literature review, I*nt J Environ Res Public Health* **2020**, 17(12):4609, doi:10.3390/ijerph17124609.
12. Villa, M. Coronavirus: la letalità in italia, tra apparenza e realtà, **2020** Milano: ISPI.
13. Justino, D.C.P.; Silva, D.F.O.; Costa, K.T.D.S.; De Morais, T.N.B.; De Andrade, F.B., Prevalence of comorbidities in deceased patients with COVID-19: A systematic review, *Med (United States)* **2022**, 101(38):e30246, doi:10.1097/MD.0000000000030246.
14. Yesudhas, D.; Srivastava, A.; Gromiha, M.M., COVID-19 outbreak: history, mechanism, transmission, structural studies, and therapeutics, *Infection* **2021**, 49(2):199-213, doi:10.1007/s15010-020-01516-2.
15. https://news.google.com/covid19/map?hl=en-US&gl=US&ceid=US%3Aen&state=1 accesed on 15 july 2023
16. Li. Y.; Ren, B.; Peng, X.; Hu, T.; Li, J.; Gong, T.; Tang, B.; Xu, X.; Zhou, X., Saliva is a non-negligible factor in the spread of COVID-19, *Mol Oral Microbiol* **2020**, 5(4):141-145, doi:10.1111/omi.12289.
17. Bloomfield, S.F.; Aiello, A.E.; Cookson, B.; O'Boyle, C.; Larson, E.L., The effectiveness of hand hygiene procedures in reducing the risks of infections in home and community settings including handwashing and alcohol-based hand sanitizers, *Am J Infect Control* **2007**, 35(10):S27-64. doi:10.1016/j.ajic.2007.07.001.
18. World Health Organization. Archived: WHO Timeline - COVID-19. Wold Heal Organ 2020.
19. Jiang, C.M.; Duangthip, D.; Auychai, P.; Chiba, M.; Folayan, M.O.; Hamama, H.H.H.; Kamnoedboon, P.; Lyons, K.; Matangkasombut, O.; Mathu-Muju, K.R.; Mathur, V.P.; Mei, M.L.; Morgan, M.; Poolthong, S.; Rahul, M.; Srinivasan, M.; Takahashi, T.; Yaklai, S.; Zhang, S.; Zou, X.C.; Chu, C.H.; Lo, E.C.M., Changes in Oral Health Policies and Guidelines During the COVID-19 Pandemic, *Front Oral Heal* **2021**, 2:668444, doi:10.3389/froh.2021.668444.
20. Clinical Research Slows as COVID-19 Surges, *Cancer Discov* **2020**, 10(5):630, doi:10.1158/2159-8290.CD-NB2020-021.
21. Hincapié, M.A.; Gallego, J.C.; Gempeler, A.; Piñeros, J.A.; Nasner, D.; Escobar, M.F., Implementation and Usefulness of Telemedicine During the COVID-19 Pandemic: A Scoping Review, *J Prim Care Community Heal* **2020**, 11:2150132720980612, doi:10.1177/2150132720980612.
22. McCullough, P.A.; Alexander, P.E.; Armstrong, R.; Arvinte, C.; Bain, A.F.; Bartlett, R.P.; Berkowitz, R.L., Berry, A.C., Borody, T.J., Brewer, J.H.; Brufsky, A.M., Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19), *Rev Cardiovasc Med* **2020**, 21(4):517-530, doi:10.31083/J.RCM.2020.04.113.
23. Luxi, N.; Giovanazzi, A.; Capuano, A.; Crisafulli, S.; Cutroneo, P.M.; Fantini, M.P.; Ferrajolo C, Moretti, U.; Poluzzi, E.; Raschi, E.; Ravaldi, C.; Reno, C.; Tuccori, M.; Vannacci, A.; Zanoni, G.; Trifirò, G.; Ilmiovaccino COVID19 collaborating group, COVID-19 Vaccination in Pregnancy, Paediatrics, Immunocompromised Patients, and Persons with History of Allergy or Prior SARS-CoV-2 Infection: Overview of Current Recommendations and Pre- and Post-Marketing Evidence for Vaccine Efficacy and Safety, *Drug Saf* **2021**, 44(12):1247-1269, doi:10.1007/s40264-021-01131-6.
24. Talic, S.; Shah, S.; Wild, H.; Gasevic, D.; Maharaj, A.; Ademi, Z.; Li, X.; Xu, W.; Mesa-Eguiagaray, I.; Rostron, J.; Theodoratou, E.; Zhang, X.; Motee, A.; Liew, D.; Ilic, D., Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: Systematic review and meta-analysis, *BMJ* **2021**, 375:e068302 doi:10.1136/bmj-2021-068302.
25. Sepúlveda-Loyola, W.; Rodríguez-Sánchez, I.; Pérez-Rodríguez, P.; Ganz, F.; Torralba, R.; Oliveira, D.V.; Rodríguez-Mañas, L., Impact of Social Isolation Due to COVID-19 on Health in Older People: Mental and Physical Effects and Recommendations, *J Nutr Heal Aging* **2020**, 24(9):938-94, doi:10.1007/s12603-020-1469-2.
26. Dhanuthai, K.; Rojanawatsirivej, S.; Thosaporn, W.; Kintarak, S.; Subarnbhesaj, A.; Darling, M.; Kryshtalskyj, E.; Chiang, C.P.; Shin, H.I.; Choi, S.Y.; Lee, S.S.; Aminishakib, P., Oral cancer: A multicenter study, *Med Oral Patol Oral y Cir Bucal* **2018**, 23(1):e23-e29 doi:10.4317/medoral.21999.
27. Zhang, X.; Liang, H.; Li, Z.; Xue, Y.; Wang, Y.; Zhou, Z.; Yu, J., Bu, Z., Chen, L., Du, Y.; Wang, X.; Wu, A.; Li, G.; Su, X.; Xiao, G.; Cui, M.; Wu, D.; Chen, L.; Wu, X.; Zhou, Y.; Zhang, L.; Dang, C.; He, Y.; Zhang, Z.; Sun, Y.; Li, Y.; Chen, H.; Bai, Y.; Qi, C.; Yu, P.; Zhu, G.; Suo, J.; Jia, B.; Li, L.; Huang, C.; Li, F.; Ye, Y.; Xu, H.; Wang, X.; Yuan, Y.; E, J.Y.; Ying, X.; Yao, C.; Shen, L.; Ji, J., Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superior, *Lancet Oncol* **2021**, 2(8):1081-1092, doi:10.1016/S1470-2045(21)00297-7.

28. Meattini, I.; Franco, P.; Belgioia, L.; Boldrini, L.; Botticella, A.; De Santis, M.C.; Marvaso, G.; Montesi, G.; Parisi, S.; Triggiani, L.; Lambertini, M.; Livi, L., Radiation therapy during the coronavirus disease 2019 (covid-19) pandemic in Italy: A view of the nation's young oncologists. *ESMO Open* **2020**, 5(2):e000779, doi:10.1136/esmoopen-2020-000779.
29. Slotman, B.J.; Lievens, Y.; Poortmans, P.; Cremades, V.; Eichler, T.; Wakefield, D.V.; Ricardi U., Effect of COVID-19 pandemic on practice in European radiation oncology centers, *Radiother Oncol* **2020**, 150:40-42, doi:10.1016/j.radonc.2020.06.007.
30. Garassino, M.C.; Whisenant, J.G.; Huang, L.C.; Trama, A.; Torri, V.; Agustoni, F.; Baena, J.; Banna, G.; Berardi, R.; Bettini, A.C.; Bria, E.; Brighenti, M.; Cadranel, J.; De Toma, A.; Chini, C.; Cortellini, A.; Felip, E.; Finocchiaro, G.; Garrido, P.; Genova, C.; Giusti, R.; Gregorc, V.; Grossi, F.; Grosso, F.; Intagliata, S.; La Verde, N.; Liu, S.V.; Mazieres, J.; Mercadante, E.; Michielin, O.; Minuti, G.; Moro-Sibilot, D.; Pasello, G.; Passaro, A.; Scotti, V.; Solli, P.; Stroppa, E.; Tiseo, M.; Viscardi G, Voltolini L, Wu YL, Zai S, Pancaldi V, Dingemans AM, Van Meerbeeck J, Barlesi F, Wakelee, H.; Peters, S.; Horn, L., COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study, *Lancet Oncol* **2020**, 21(7):914-922, doi:10.1016/S1470-2045(20)30314-4.
31. Soroosh, D.; Javadinia, S.A., The COVID-19 outbreak and oncology centers in Iran, *Int J Cancer Manag* **2020**, 13(6), doi:10.5812/ijcm.103283.
32. DeVita, V.T.; Lawrence, T.S.; Rosenberg, S.A., DeVita, Hellman, and Rosenberg's cancer: Principles & practice of oncology, *Lippincott Williams & Wilkins* **2018**,2.
33. Deshmukh, V.; Motwani, R.; Kumar, A.; Kumari, C.; Raza, K, Histopathological observations in COVID-19: A systematic review, *J Clin Pathol* **2021**, 74(2):76-83, doi:10.1136/jclinpath-2020-206995.
34. Andrews, P.L.R.; Cai, W.; Rudd, J.A.; Sanger, G.J., COVID-19, nausea, and vomiting, *J Gastroenterol Hepatol* **2021**, 36(3):646-656, doi:10.1111/jgh.15261.
35. Tian, J.; Yuan, X.; Xiao, J.; Zhong, Q.; Yang, C.; Liu, B.; Cai, Y.; Lu, Z.; Wang, J.; Wang, Y.; Liu, S.; Cheng, B.; Wang, J.; Zhang, M.; Wang, L.; Niu, S.; Yao, Z.; Deng, X.; Zhou, F.; Wei, W.; Li, Q.; Chen, X.; Chen, W.; Yang, Q.; Wu, S.; Fan, J.; Shu, B.; Hu, Z.; Wang, S.; Yang, X.P.; Liu, W.; Miao, X.; Wang, Z., Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study, *Lancet Oncol* **2020,** 21(7):893-903, doi:10.1016/S1470-2045(20)30309-0.
36. Yang, K.; Sheng, Y.; Huang, C.; Jin, Y.; Xiong, N.; Jiang, K.; Lu, H.; Liu, J.; Yang, J.; Dong, Y.; Pan, D.; Shu, C.; Li, J.; Wei, J.; Huang, Y.; Peng, L.; Wu, M.; Zhang, R.; Wu, B.; Li, Y.; Cai, L.; Li, G.; Zhang, T.; Wu, G., Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study, *Lancet Oncol* **2020**, 21(7):904-913, doi.org:10.1016/S1470-2045(20)30310-7.
37. Shams, S.; Mansoor, K., COVID-19 and Self-Care Measures by Chemotherapy Patients. Asia-Pacific, *J Oncol Nurs* **2020**, 7(4):310-311, doi:10.4103/apjon.apjon_20_20.
38. Al-Shamsi, H.O.; Alhazzani, W.; Alhuraiji, A.; Coomes, E.A.; Chemaly, R.F.; Almuhanna, M.; Wolff, R.A.; Ibrahim, N.K.; Chua, M.L.K.; Hotte, S.J.; Meyers, B.M.; Elfiki, T.; Curigliano, G.; Eng, C.; Grothey, A.; Xie, C., A Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group, *Oncologist* **2020**, 25(6):e936-e945 , doi:10.1634/theoncologist.2020-0213.
39. Kanjanapan, Y.; Yip, D., Considerations for cancer immunotherapy during the COVID-19 pandemic, *Med J Aust* **2020**, 213(9):390, doi:10.5694/mja2.50805.
40. Akula, S.M.; Abrams, S.L.; Steelman, L.S.; Candido, S.; Libra, M.; Lerpiriyapong, K.; Cocco, L.; Ramazzotti, G.; Ratti, S.; Follo, M.Y.; Martelli, A.M.; Blalock, W.L.; Piazzi, M.; Montalto, G.; Cervello, M.; Notarbartolo, M.; Basecke, J.; McCubrey, J.A., Cancer therapy and treatments during COVID-19 era, *Adv Biol Regul* **2020**, 77:100739, doi:10.1016/j.jbior.2020.100739.
41. Di Molfetta, S.; Feola, T.; Fanciulli, G.; Florio, T.; Colao, A.; Faggiano, A. Immune Checkpoint Blockade in Lung Carcinoids with Aggressive Behaviour: One More Arrow in Our Quiver?, *J Clin Med* **2022**, 11(4):1019, doi:10.3390/jcm11041019.
42. Liu, C.; Wang, M.; Zhang, H.; Li, C.; Zhang, T.; Liu, H.; Zhu, S.; Chen, J., Tumor microenvironment and immunotherapy of oral cancer, *Eur J Med Res* **2022**, 27(1):198, doi:10.1186/s40001-022-00835-4.
43. Serra-García, L.; Bosch-Amate, X.; Alamon-Reig, F.; Giavedoni, P.; Fuertes, I.; Morgado-Carrasco, D.; Iglesias, P.; Puig, S.; Mascaró, J.M, Jr., Digital ischemia triggered by coronavirus disease 2019 in a patient under cemiplimab treatment, *Int J Dermatol* **2021**, 60(1):e30-e32, doi:10.1111/ijd.15239.
44. Takenaka, M.; Nakamori, M.; Ishikawa, R.; Aoki, S.; Maruyama, H., Encephalopathy after COVID-19 vaccination during treatment with nivolumab: A case report, *Clin Neurol Neurosurg* **2023**, 226:107632, doi:10.1016/j.clineuro.2023.107632.
45. Ying, Z.; Huang, X.F.; Xiang, X.; Liu, Y.; Kang, X.; Song, Y, Guo, X., Liu, H., Ding, N., Zhang, T. and Duan, P., A safe and potent anti-CD19 CAR T cell therapy, *Nat Med* **2019**, 25(6):947-953, doi:10.1038/s41591-019-0421-7.
46. Gorchakov, A.A.; Kulemzin, S. V.; Kochneva, G.V.; Taranin, A.V., Challenges and Prospects of Chimeric Antigen Receptor T-cell Therapy for Metastatic Prostate Cancer, *Eur Urol* **2020**, 77(3):299-308, doi:10.1016/j.eururo.2019.08.014.
47. Atanackovic, D.; Luetkens, T.; Omili, D.; Iraguha, T.; Lutfi, F.; Hardy, N.M.; Fan, X.; Avila, S.V.; Saharia, K.K.; Husson, J.S,; Niederhaus, S.V.; Margiotta, P.; Lee, S.T.; Law, J.Y.; Mannuel, H.D.; Vander Mause, E.; Bauman, S.; Lesho, P.; Hankey, K.; Baddley, J.; Kocoglu, M.; Yared, J.A.; Rapoport, A.P.; Dahiya, S., Vaccine-induced T-cell responses against SARS-CoV-2 and its Omicron variant in patients with B cell–depleted lymphoma after CART therapy, *Blood* **2022**, 140(2):152-156, doi:10.1182/blood.2022016175.
48. Oh, B.L.Z.; Tan, N.; de Alwis, R.; Kunasegaran, K.; Chen, Z.; Poon, M.; Chan, E.; Low, J.G.H.; Yeoh, A.E.J.; Bertoletti, A.; Le Bert, N., Enhanced BNT162b2 vaccine-induced cellular immunity in anti-CD19 CAR T cell–treated patients, *Blood* **2022**, 140(2):156-160 doi:10.1182/blood.2022016166.
49. Auletta, J.J., Buckling up against COVID-19 after CAR T-cell therapy, *Blood* **2022**, 140(2):85-87, doi:10.1182/blood.2022016855.