



## CHALLENGES DURING COVID-19 PANDEMIC: THE MANAGEMENT AND VACCINATION OF THE ONCOLOGIC PATIENT

Diana-Lavinia PRICOPE <sup>a</sup>, Bogdan-Ionuț PRICOP <sup>c</sup> and Cornelia AMĂLINEI <sup>a, d</sup>

<sup>a</sup>Department of Morphofunctional Sciences I- Histology, “Grigore T. Popa” University of Medicine and Pharmacy, Iasi, Romania

<sup>b</sup>Regional Institute of Oncology, Iasi, Romania

<sup>c</sup>NHS Grampian, Aberdeen, United Kingdom

<sup>d</sup>Department of Histopathology, Institute of Legal Medicine Iasi, Romania

Corresponding author: Email: dianalavinia64@gmail.com, dianalavinia825@gmail.com

Accepted January 22, 2021

The COVID-19 pandemic, the most important health crisis of the last few decades, has been causing significant disruptions with regard to medical care access. It has overwhelmed healthcare systems worldwide at a scale never seen before. This was because the virus has a high transmission rate on one side, and elderly patients or those with comorbidities, such as cancer, frequently developed a severe form of the disease, on the other. Furthermore, the SARS-CoV-2 pandemic in itself has limited the access of oncologic patients to proper healthcare. In this context, a decreased number of follow ups per patient, along with an overall worsen prognosis has been registered. One reason for this was, and still is, that geriatric patients or those with other diseases, like cancer, frequently developed a severe form of the disease. The availability of a safe and efficient vaccine creates the premises for improved management and prognosis of oncologic patients. This article aims to review the available literature, in order to better understand the impact of the novel coronavirus on the treatment and diagnosis of cancer patients, and to find what solutions have been implemented in this regard.

*Key words:* cancer, oncologic patient, COVID-19, immunosuppression, vaccination.

### INTRODUCTION

COVID-19 has become a major national and international challenge for the medical community. The high transmission rate of this virus, even during the asymptomatic stage of the disease, has determined the rapid widespread to a pandemic level. Moreover, this disease has a broad range of manifestations, varying from asymptomatic or mild, flu-like forms, to severe cases of COVID-19 pneumonia<sup>1</sup>. This type of pneumonia is life-threatening, requires oxygen therapy and some form of respiratory support<sup>1</sup>, either invasive or non-invasive, depending on the severity of the disease.

The new coronavirus, otherwise known as SARS-CoV-2 or severe acute respiratory syndrome coronavirus 2, is part of the betacoronavirus subgenus<sup>2</sup>. Other viruses from the same group, SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) caused serious outbreaks in 2002 and 2015 respectively, all of

them having a zoonotic origin<sup>3</sup>. Knowing this, a great part of the medical research done in the last year was aimed to the understanding of the pathogenesis of COVID-19. It was discovered that the key element for its high infection rate is the ACE2 (angiotensin converting enzyme 2). In this context, the enzyme acts as a cell-membrane receptor, with a high affinity for the virus<sup>4</sup>.

The ACE2 is widely expressed in the human body. The epithelial cells of the alveoli have a high expression rate, which explains the pulmonary symptoms of the disease<sup>4</sup>. It was discovered that the severity of the illness depends on age, other comorbidities and ACE2 expression<sup>4</sup>. This enzyme also increases with age and the presence of chronic diseases<sup>4</sup>. Some studies revealed that cancer patient have a higher risk of developing a severe form of SARS-CoV-2, not only because they are immunocompromised, but also because their ACE2 expression was greater<sup>4</sup>.

When it comes to SARS-CoV-2 and cancer patients, it is clear that they are more vulnerable than other categories<sup>3</sup>. This is not only due to their higher risk of having a severe form of COVID-19,

but also because the coronavirus infection can aggravate the existent neoplastic disease<sup>1</sup>. On top of this, the restrictions imposed to limit the spread of the new coronavirus are raising the anxiety levels associated with the oncological diagnosis and treatment<sup>5</sup>. The continuous need for therapy in oncology, such as surgical procedures, chemo-radiotherapy, immunotherapy or biological therapy, made the medical staff realise that these patients require a form of continuous medical supervision<sup>5</sup>, which seems to be achievable *via* SARS-CoV-2 vaccination.

Considering the influence of the current pandemic over the healthcare system, the available scientific data is attesting the challenges of COVID-19 infection over an already immunocompromised patient<sup>6</sup>. The clinical experience attained during the pandemic raises concerns with regard to maintaining the same, proper care plan for cancer patients as before this new coronavirus, as well as with having a similar outcome<sup>6</sup>. One possible answer to this dilemma is an efficient vaccination plan for this risk category.

## OBJECTIVES

Our review's purpose is to evaluate the pandemic's effects over the general prognosis in oncology and to find feasible solutions, by studying the available scientific papers. The search was restricted to human studies and the published literature from 2020 to present time. In order to find suitable studies, we performed an online search through general bibliographic databases, mainly PubMed and Scopus, to identify relevant articles which reported on the management of cancer patients in the era of SARS-CoV-2. The search was performed using the following descriptors: "cancer", "oncologic patient", "COVID-19", "immunosuppression", "vaccine" and was limited to the literature published in English and the reported data has been evaluated by comparison with our experience.

## RESULTS AND DISCUSSIONS

All studies relevant for the selected topic reported the impact of the COVID-19 pandemic on oncologic patients and highlighted the importance of prioritized vaccination for this populational group. Other findings have been grouped into several categories which may compose a picture of

the practical difficulties encountered in the management of these patients.

## THE WAY CANCER IS BEING DIAGNOSED DURING COVID-19 PANDEMIC

The quality of life and long-term survivability rate of oncologic patients depend upon reaching an accurate diagnosis and cancer staging as soon as possible<sup>6</sup>. This is necessary in order to provide the proper treatment as swift as possible, with the intention of maximizing the chances of remission (ideally) or to prologue survivability while maintaining a as close to normal quality of life<sup>6</sup>.

Cancer screening programmes suffered changes as well<sup>7</sup>. Before the pandemic, many individuals were able to uncover silent malignancies because of them, especially early-stage cancers, which offered a great prognosis<sup>7</sup>. But as a result of COVID-19, some countries, such as the United Kingdom, suspended their screening programmes for cancers<sup>7</sup>.

There were studies which highlighted that some common blood test results, such as the full blood count, raised some diagnostic challenges. For example, there were cases in which leucocytosis associated with either neutrophilia or lymphocytosis were correlated with COVID-19 infection, and that concealed a malignant blood disorder<sup>6</sup>. The opposite situation was also possible, when blood changes specific to a certain malignant disease hid an asymptomatic coronavirus infection<sup>6</sup>. This was the case of a patient, with a past history of non-Hodgkin lymphoma, whose latest blood test changes and cough were attributed to a recurrence of the cancer, when in fact he only suffered from SARS-CoV-2<sup>6</sup>. Other changes, such as those specific to febrile neutropenia can be easily mistaken with an infection from the new coronavirus. These include fever, shortness of breath or diarrhoea<sup>5</sup>.

Some of the clinical signs and symptoms of pulmonary cancer, like coughing, polypnea or a general loss in pulmonary function, overlap with those of the novel coronavirus infection<sup>1</sup>. In some studies, there were issues with reaching a proper diagnosis for those patients with pulmonary neoplasia, due to this condition<sup>1</sup>.

## ONCOLOGIC PATIENT – A HIGH-RISK CATEGORY

The association between pathologies such as type 2 diabetes, cardiovascular disease, Chronic

obstructive pulmonary disease (COPD) or cancers significantly increase the vulnerability for COVID-19 related complications<sup>5</sup>. Active malignancy in itself constitutes a high risk for developing a severe form of coronavirus infection<sup>5</sup>. This is due to a compromised immune system caused by the cancer on one side and the antitumoral treatment on the other<sup>5</sup>. Studies show that the infection with SARS-Cov-2 in cancer patients has doubled death rates<sup>6</sup>. In a hospital from Italy for example, out of the deaths caused by coronavirus pneumonia, 27% had a malignancy<sup>6</sup>.

There are a series of risk factors which showed to offer a poorer prognostic and a higher chance of developing a severe form of COVID-19 in patients with malignant tumours<sup>8</sup>. The most important ones are old age, deteriorated ECOG (Eastern Cooperative Oncology Group) performance status, active (or remitted) malignancy, an already advanced stage of neoplasia, antineoplastic medication, as well as some genetic factors like ACE2 and TMPRSS2 (Transmembrane protease serine type 2) polymorphism, which influences the easiness with which the virus attaches to the cell membrane<sup>8</sup>.

Studies from the USA and Canada have evaluated potential prognosis factors for cancer patients with COVID-19<sup>9</sup>. The elements analysed at the enrolled individuals were the type of malignancy, age, sex, obesity and whether they were smokers or non-smokers<sup>9</sup>. It was discovered that the cancers with the highest frequency among those infected with the novel coronavirus were the cancers of the breast, lungs and prostate<sup>9</sup>. The research included a cohort of 928 individuals, with an average age of 66 years old and contained an equal number of males and females<sup>9</sup>. Although race, ethnicity, obesity or the type of cancer were not correlated with the death rate in this study, the thirty day all-cause mortality was high<sup>9</sup>.

Another research paper from the United Kingdom tracked all-cause mortality in cancer patients, which were also receiving oncologic treatment<sup>9</sup>. The study included 800 people, out of which 52% had mild coronavirus symptoms, while 28% had severe forms<sup>9</sup>. The mortality rate was associated with old age, the male gender, cardiovascular disease<sup>9</sup>. The cancer treatment itself (immunotherapy and hormonotherapy) did not appear to have affected the death rate<sup>9</sup>.

## THE MANAGEMENT OF ONCOLOGIC PATIENTS DURING COVID-19 PANDEMIC

Cancer patients are a distinct group of people, from a healthcare perspective, due to their therapy

requirements<sup>5</sup>. They are in need of continuous outpatient care, which includes frequent evaluation and treatment<sup>5</sup>. However, being a high-risk category, oncologic patients (and their doctors) must follow a series of safety rules in order to avoid infection with the new coronavirus, rules which alters the way they receive care today<sup>10</sup>. As a result, the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) has developed the “ESMO management and treatment adapted recommendations in the COVID-19 era” guidelines<sup>4</sup>. These recommendations offer guidance for the prioritisation of various cancer patients accordingly to their specific medical needs. For example, the patients who require immediate and long-term care are of top priority as they have a favourable risk-benefit ratio: the advantages of receiving continuous medical care trumps the risks raised by the pandemic<sup>4</sup>. The individuals included in this category are those with either a rapid growth-rate cancer, a high risk of death, febrile neutropenia, as well as patients who can receive curative treatment or treatment that improves their long-term prognosis<sup>4</sup>.

In the largest facility for oncologic patients in our region, the pandemic imposed the introduction of various restrictions as per the ESMO (European Society for Medical Oncology) guidelines. Some of these involved the changing of IV chemotherapy regimens with oral where possible, without making a compromise with regard to the efficacy of the treatment, such as replacing 5-Fluorouracil with Capecitabine for colorectal or other types of cancers. Another was the implementation of telemedicine for those who had to travel long distances to the Institute for a consultation.

Other oncologic centres had to take similar measures to stop the spread of COVID-19. For example, a multi-centric randomised study from Sweden demonstrated that delaying TME (total mesorectum excision) surgeries for stage II-III locally advanced colorectal cancers was a viable option<sup>11, 12</sup>. Instead of having the surgery immediately after radiotherapy, it was delayed up to 8 weeks and the study results showed a better response than the initial approach<sup>12</sup>. This analysis was done on 840 participants with locally advanced colorectal cancer and the data was collected from Swedish ColoRectal Cancer Registry<sup>12</sup>. Another multi-centric study from France for the same type of cancer, GRECCAR-6 (a multicentric randomized controlled trial), showed an increased morbidity rate if TME was

delayed with more than 11 weeks<sup>11</sup>. Furthermore, the surgical margins had a higher risk of being compromised (complete TME 78.7% *versus* 90%)<sup>11, 13</sup>. In other words, no delay beyond 8 weeks is recommended if long-course radiotherapy is included in the treatment plan<sup>11, 13</sup>.

The management of the majority of the neoplasms requires a multidisciplinary approach and the surgeons are usually a part of the multidisciplinary team<sup>10</sup>. In some types of cancer, especially in early stages, a surgical procedure can offer the cure. But there are cases in which this can be rescheduled, as long as this does not raise a risk for disease progression. Le Comité de Cancérologie de l'Association Française d'Urologie (CTAUF) published a series of recommendations when it comes to urological cancers<sup>6</sup>. In the case of prostate cancer, for those in the early-stage and with a low risk, they suggest a monitoring approach, while for an advanced stage, with an intermediate risk, they argue for hormonal therapy associated with radiotherapy<sup>6</sup>. For early-stage kidney cancer, CTAUF guidelines suggests maintaining chemotherapy and postponing surgery, while for bladder cancer, if it is operable, the use of neoadjuvant chemotherapy in association with G-CSF haematopoietic factor is proposed, in order to avoid febrile neutropenia<sup>6</sup>.

Radiotherapy has proven itself to be reliable for various malignancies<sup>5</sup>. These include early-stage gynaecological, ENT (ear, nose and throat) or colorectal cancers, as well as for those who are locally advanced or in advanced stages but as palliative treatment<sup>5</sup>. Unfortunately, the COVID-19 pandemic has imposed the need to reduce the number of patients which receive radiotherapy, due to social distancing requirements. As a result, the patients which should be prioritised are those with a potentially curable malignancy, or those with a rapid growth-rate tumour<sup>4</sup>. This is because radiotherapy can convert a locally advanced inoperable cancer (*e.g.*, colorectal) into an operable one, affecting survival rates in a meaningful way.

Similar guidelines are offered by other societies as well. Several French societies (Société Française de Chirurgie Oncologique SFCO, Société Française de Sénologie et Pathologie Mammaire SFSPM and French Breast Cancer Intergroup-UNICANCER UCBG) are advising to maintain screening for breast cancer, to continue adjuvant and neoadjuvant radiotherapy for patients with good performance status but within hypofractionated regimens, to use oral chemotherapy where possible and to avoid difficult breast

reconstruction surgery<sup>6</sup>. Another French group, FRANCOGYN, suggests replacing surgery with radio-chemotherapy in cervical cancer as a first line, while for operable ovarian cancer, to use chemotherapy as an alternative to surgery<sup>6</sup>.

The new pandemic has led to postponing many dermatological consultations, which caused a drop in the diagnosis of melanoma. According to the new changes to the guidelines for this cancer, the treatment for stage T0 and T1 melanoma can be delayed, as long as there is no residual macroscopic disease. For stage T2 and above, a three-month treatment delay is acceptable, if the margins of the biopsy are negative<sup>14</sup>.

### **A SPECIAL CATEGORY: PULMONARY CANCER PATIENTS**

The individuals with lung cancer have a higher risk of developing a severe form of SARS-CoV-2, due to their poor pulmonary function. Studies from China, which assessed the impact of this novel virus on patients with malignancies, showed that the most frequent type of cancer among those enrolled was the bronchopulmonary type<sup>8</sup>. It was not clear if this was because of their increased susceptibility to the virus or if this type of neoplasia was simply more common<sup>8</sup>.

Various Chinese expert groups (Lung Cancer Study Group, Chinese Thoracic Society, Chinese Medical Association, and Chinese Respiratory Oncology Collaboration) advocate for, where possible, the treatment of NSCLC (Non-small-cell lung carcinoma) patients in outpatient facilities, or to test for COVID-19 where inpatient care is mandatory<sup>8</sup>. They make recommendations for the medical personnel to keep in mind, for lung cancer patients, the possibility of an associated respiratory infection (viral or otherwise)<sup>8</sup>. Radiation pneumonitis or that determined by immunotherapy should also not be forgotten as these could easily be mistaken for SARS-CoV-2. Similar suggestions were made by the Radiological Society of North America as well. They have observed that some chest CT scans changes, suggestive for COVID-19 infection, can be found in other pathologies as well<sup>15</sup>. One example is the bilateral ground-glass opacification, which can also appear as a reaction to radiotherapy or immunotherapy. Testing for the new coronavirus is of paramount importance for these patients<sup>15</sup>.

## VACCINATION AMONG IMMUNOCOMPROMISED CANCER PATIENTS

Vaccines have been proven, time and again, to be a valuable tool against various infectious illnesses<sup>16</sup>. Unfortunately, individuals with immunocompromising conditions cannot fully benefit from this discovery<sup>16</sup>, as their immune response is generally reduced. In these individuals, vaccines produce a lower level of protection and have a higher risk of adverse effects, especially in the case of live attenuated vaccines (LAV)<sup>17,18</sup>. As a result, alternatives such as vaccines containing purified antigens, inactivated organisms or mRNA are recommended, since they have a suitable safety profile and no increased risk of side effects, when compared to LAV<sup>17,18</sup>.

mRNA has been produced in vitro for about 10 years but using this technology for vaccine production was not viable until recently<sup>19</sup>. Novel innovations in fast, large-scale mRNA production methods, sequence engineering and in the development of efficient delivery materials has made this possible<sup>20</sup>. The new delivery system, the nanoparticles, have the properties such as high loading efficiency, enhanced permeation and others, which improves the vaccine's immunogenicity<sup>20,21</sup>. The mRNA vaccine has an improved safety profile and a higher efficiency in generating an immune response, when compared to some older technologies<sup>19,20</sup>. Moreover, since it does not contain any viral particles, it cannot cause any form of the disease against which was made, when compared to LAV<sup>23</sup>. This is because an mRNA vaccine helps the body to only mimic the disease antigen in order to stimulate an immune response<sup>20</sup>. Being such a new technology, mRNA vaccine technology is still in its infancy, but the potential it shows can generate a whole new era of vaccination against various diseases, including some types of cancer<sup>23,24</sup>.

Cancer patients are part of this high-risk group. This is especially because a main adverse effect of chemotherapy is immunosuppression, which can last for the full course of treatment and even go on for up to 6 to 12 months after therapy<sup>17</sup>, in addition to the effects of the malignancy itself. We must also keep in mind that their treatment requirements compel them to have contact with a high number of people. Therefore, there is a general proposal that this group of patients must have priority for the novel coronavirus vaccine. This prioritization

has been made for their own protection and also to prevent the spread of this virus, as these patients have a higher chance of transmitting the infection<sup>22</sup>. A serious challenge of COVID-19 is the risk of reinfection. There are studies which suggest that a second SARS-CoV-2 infection can be worse than the first one<sup>23,25</sup>. This raises questions with regard to the effectiveness of the immune response generated either by the disease or the vaccine and how long will it last<sup>22,23</sup>. Research is still needed to find these answers since the virus and especially the vaccine is fairly new.

## CONCLUSIONS

The current pandemic still remains a serious challenge for any healthcare system. Much research is still needed to uncover the complete mechanism of interaction between the new coronavirus and the immune system, as well as the long-term efficacy of the immune response generated either by a vaccine or infection. Until then, cancer patients must be shielded, as a high-risk category. Various protocols have been developed having this in mind and should be implemented where possible. Individual with malignancies should be encouraged to get vaccinated against SARS-COV-2 virus, but a final decision should be made in collaboration with the oncologist. The high efficacy and safety of mRNA vaccines should be considered when making this decision.

## REFERENCES

1. Al-Quteimat, Amer O.M., *The impact of the COVID-19 pandemic on cancer patients. Am J Clin Oncol* **2020**; 43(6): 452-455.
2. Samudrala, P. K., *Virology, pathogenesis, diagnosis and in-line treatment of COVID-19. Eur J Pharmacol* **2020**; 883: 173375.
3. Melenotte, C., *Immune responses during COVID-19 infection. Oncoimmunology* **2020**; 9(1): 1807836.
4. Gosain, R., *COVID-19 and cancer: a comprehensive review. Curr Oncol Rep* **2020**; 22(5): 53.
5. van de Haar, J., *Caring for patients with cancer in the COVID-19 era. Nat Med* **2020**; 26(5): 665-671.
6. Moujaess, E., *Cancer patients and research during COVID-19 pandemic: A systematic review of current evidence. Crit Rev Oncol Hematol* **2020**; 150: 102972.
7. Weller, D., *Cancer diagnosis and treatment in the COVID-19 era. Eur J Cancer Care (Engl)* **2020**; 29(3): e13265. 7
8. Al-Shamsi, H. O., *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.
9. Akula, S. M., *Cancer therapy and treatments during COVID-19 era. Adv Biol Regul* **2020**; 77: 100739.
  10. Curigliano, G., *Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol* **2020**; 31(10): 1320-1335.
  11. Li, Y., *A review of neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Int J Biol Sci* **2016**; 12(8): 1022-1031.
  12. Erlandsson, J., *Tumour regression after radiotherapy for rectal cancer - results from the randomised Stockholm III trial. Radiother Oncol* **2019**; 135: 178-186.
  13. Skowron, K. B., *Caring for patients with rectal cancer during the COVID-19 pandemic. J Gastrointest Surg* **2020**; 24(7): 1698-1703.
  14. Baumann, B. C., *Management of primary skin cancer during a pandemic: multidisciplinary recommendations. Cancer* **2020**; 126(17): 3900-3906.
  15. Dingemans, A. C., *Treatment guidance for patients with lung cancer during the coronavirus 2019 pandemic. J Thorac Oncol* **2020**; 15(7): 1119-1136.
  16. Ribas, A., *Priority COVID-19 vaccination for patients with cancer while vaccine supply is limited. Cancer Discov* **2021**; 11(2): 233-236.
  17. Martire, B., *Vaccination in immunocompromised host: recommendations of Italian Primary Immunodeficiency Network Centers (IPINET). Vaccine* **2018**; 36(24): 3541-3554.
  18. Varghese, L., *Contraindication of live vaccines in immunocompromised patients: an estimate of the number of affected people in the USA and the UK. Public Health* **2017**; 142: 46-49.
  19. Pardi, N., *Recent advances in mRNA vaccine technology. Curr Opin Immunol* **2020**; 65: 14-20.
  20. Ho, W., *Next-generation vaccines: nanoparticle-mediated DNA and mRNA delivery." Adv Healthc Mater* **2021**; e2001812.
  21. Lee, N. and McGeer A., *The starting line for COVID-19 vaccine development. Lancet* **2020**; 395(10240): 1815-1816.
  22. Raymond, E., *Impact of the COVID-19 outbreak on the management of patients with cancer. Target Oncol* **2020**; 15(3): 249-259.
  23. Bettini, E., Locci, M. *SARS-CoV-2 mRNA Vaccines: immunological mechanism and beyond. Vaccines.* **2021**; 9(2):147.
  24. Shin, M. D., *COVID-19 vaccine development and a potential nanomaterial path forward. Nat Nanotechnol* **2020**; 15(8): 646-655.
  25. Wang, J., *The COVID-19 vaccine race: challenges and opportunities in vaccine formulation. AAPS PharmSciTech* **2020**; 21(6): 225.