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*Coronavirus Pandemic*

# Clinical analysis of COVID-19 positive cancer inpatients in National Cancer Center in Serbia

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## Abstract

Introduction: The outbreak of COVID-19 has had an impact on global healthcare as well as on radiotherapy practice in many countries. This study aimed to identify clinical characteristics of Coronavirus Disease 2019 (COVID-19) infected cancer inpatients, as well as what impact this infection had on radiation treatment of the patients.

Methodology: In this retrospective study, we included cancer inpatients with laboratory confirmed COVID-19 infection during the radiotherapy or chemoradiation in April 2020 in National Cancer Research Center in Serbia. Data were obtained from the medical records between 1 April and 1 July 2020.

Results: A total of 49 COVID-19 infected cancer inpatients were included. The most frequently reported cancers were head and neck cancers, in twenty-three patients (46.8%). Lymphopenia was present in 77.5% of the patients. Red blood cells, haemoglobin and platelets were significantly lower during incubation or diagnosis of COVID-19. Twenty-seven (55.1%) patients did not finish radiotherapy. The age of patients who finished radiotherapy after COVID-19 infection was significantly lower compared to the patients who did not finish radiotherapy (60.5 ± 7.8 vs. 68.6 ± 11.2; $p < 0.005$).

Conclusions: COVID-19 infected cancer patients in radiotherapy practice show similar symptoms and demographic characteristics as the general population infected with SARS-CoV-2 virus. Patients with head and neck cancers may be susceptible to infection with COVID-19. Old age and male gender may be risk factors for discontinuation of radiotherapy in COVID-19 infected cancer patients.

**Key words:** COVID-19; Infection; Cancer; Radiotherapy.

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## Introduction

A novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified in December 2019, in China, and rapidly spread through the world causing a pandemic. As of January 19th 2021, 96,382,448 positive cases of COVID-19 have been reported, with 2,058,733 COVID 19-related deaths worldwide [1]. On the same date, the total number of COVID-19 positive cases in Serbia was 375,799 with 3,791 deaths. Clinical presentation may vary from asymptomatic patients to severe pneumonia and among others, complications include acute respiratory distress syndrome, acute cardiac injury and secondary infection [2]. Patients with cancer may experience severe COVID-19-related outcomes as they are considered to be particularly vulnerable to SARS-CoV-2 [3]. Not all the cancer treatment modalities need have the same impact and the same risk of morbidity in these patients [4]. The outbreak of COVID-19 has had an impact on global healthcare as well as on radiotherapy practice in many countries. Some of the countries reorganized their practice through modification of radiotherapy (RT) treatment as well as with administrative changes [5]. Available data on risk and morbidity of COVID-19 positive patients with cancer are different. We aimed to analyse the clinical characteristics of COVID-19 infected cancer inpatients in radiotherapy practice to provide more information about the clinical behaviour and outcome of these patients and what effect this infection may have for the treatment of patients with cancer.

## Methodology

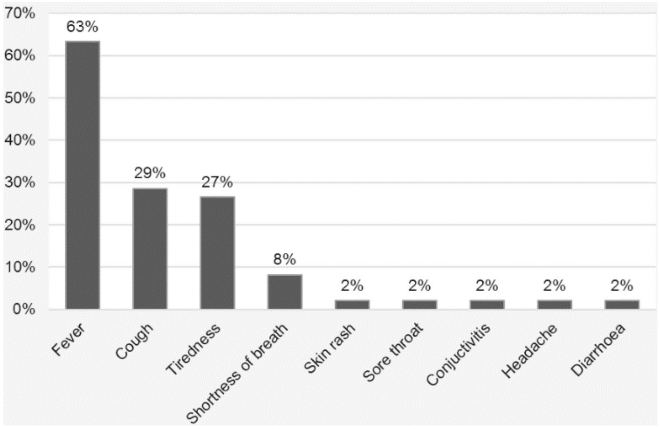
A total of eighty-nine patients were hospitalized at the Department of Radiotherapy of Solid Tumors, at the Institute of Oncology and Radiology of Serbia for radiation or chemoradiation in April 2020. Forty-nine cancer patients who were presented with COVID-19

during hospitalization in April 2020 were identified and retrospectively analysed. COVID-19 infection was confirmed after nasopharyngeal swabs on a reverse-transcriptase-polymerase-chain reaction (RT PCR) assay. COVID-19 related pneumonia was diagnosed either with chest-X-ray radiography or computed tomography (CT) scan. Radiation therapy or chemoradiation were immediately stopped after COVID-19 diagnosis. Clinical retrospective data were obtained from the medical records in the period between 1 April and 1 July 2020. Data about treatment of COVID-19 infection were not showed as these patients were referred for the treatment in COVID-19 medical centers soon after the diagnosis of SARS-CoV-2 infection was established. An analysis of categorical variables was performed using the Chi-square test. Kolmogorov-Smirnov tests were employed to determine if the distribution of the age and lactate dehydrogenase (LDH) as continuous variable was normal. The Student t-test was employed to compare age of patients and LDH activity with finished RT and those who did not complete RT after the treatment of COVID-19 infection. Univariate binary logistic regression analysis was applied for the estimation of parameters' ability to predict the course of RT. All statistical analyses were carried out using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA), and results were considered statistically significant where two-tailed P-value was less than 0.05. Data are shown as mean ± standard deviation for continuous variable and relative and absolute frequencies for categorical variables. This study was approved by the local ethical committee.

**Table 1.** Demographic and clinical features of COVID-19 positive cancer inpatients.

| **Patient data** | |
|---|---|
| **Age, years** | 64.2 ± 10.6 |
| **Gender** | **n (%)** |
| Male | 40 (82) |
| Female | 9 (18) |
| **Cancer** | |
| Lung cancer | 4 (8.2) |
| Brain tumor | 9 (18.6) |
| Hypopharyngeal cancer | 5 (10.2) |
| Lingual cancer | 5 (10.2) |
| Unknown primary tumors of the head and neck | 1 (2.0) |
| Carcinomas of the lip and oral cavity | 3 (6.1) |
| Laryngeal cancer | 3 (6.1) |
| Oropharyngeal cancer | 3 (6.1) |
| Nasopharyngeal cancer | 3 (6.1) |
| Prostate cancer | 7 (14.3) |
| Colorectal cancer | 5 (10.2) |
| Stomach cancer | 1 (2.0) |
| **Radiotherapy** | |
| Definitive | 16 (33) |
| Postoperative | 22 (45) |
| Preoperative | 7 (14) |
| Palliative | 3 (6) |
| Craniospinal | 1 (2) |
| **Chemoradiation** | |
| No | 20 (41) |
| Yes | 29 (59) |
| **ECOG PS*** | |
| 0 | 15 (31) |
| 1 | 29 (59) |
| 2 | 5 (10) |

**Figure 1.** The frequency of symptoms of 49 COVID-19 positive cancer inpatients.




## Results

Descriptive characteristics of the 49 cancer patients at the Department for Radiotherapy of Solid Tumours in Serbia with confirmed COVID-19 infection in April 2020 are shown in detail in Table 1. The mean age (±SD) of the patients was 64.2 ± 10.6 years (range 27-83). Forty (82%) patients were male. The most frequently reported cancers were head and neck cancers (46.8%). Twenty-two patients (45%) received adjuvant radiation treatment. Fifty-nine percentage of the cancer patients received chemoradiation. Forty-three (87.8%) patients were in active radiation treatment. Figure 1 shows the frequency of symptoms. The most common symptom in our patients was fever. Other symptoms were less common and not a single patient had a loss of sense of smell and taste. Fourteen (28.5%) patients developed pneumonia.

According to laboratory findings, lymphopenia was present in 38 (77.5%) patients and leucopenia was present in 16 (32.6%) patients during incubation or diagnosis of SARS-CoV-2. Analysing baseline values (before RT) of white blood cells (WBC) and lymphocytes and values during the incubation or diagnosis of COVID-19 there was no statistical

difference between them. Elevated levels of LDH were found in 6 (12.2%) patients. High levels of C-reactive protein were documented in 31 (63.2%) patients during incubation or diagnosis of SARS-CoV-2, while for 15 patients there was no available information about the levels of C-reactive protein.

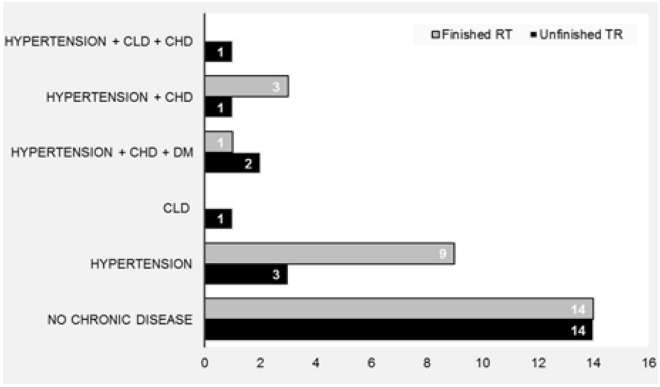
In addition to cancer, the most frequent chronic medical condition was hypertension, in 20 (40.8%) patients, followed by heart diseases and rhythm disorders in 8 (16.3%) patients. Diabetes had 3 (6.1%) patients.

As the main event we observed was whether patients completed radiation therapy after the treatment of COVID-19 infection, we further investigated coexisting factors such as chronic diseases, age, and laboratory parameters to determine potential causes of the uncompleted RT. The patients were divided in two groups: patients who finished RT (n=22) despite COVID-19 infection and those who did not finish RT (n=27). When we compared the obtained data regarding chronic diseases, there were no significant differences in the distribution between these two groups (Figure 2). However, there were a significant difference between laboratory results range distribution before RT and during incubation or diagnosis of COVID-19 in the terms of anaemia and lower platelets count (Table 2).

Additionally, the age of patients who finished RT was significantly lower compared to patients who did not finish RT (60.5 ± 7.8 vs. 68.6 ± 11.2; p<0.005). The LDH activity did not show significant differences among patients with finished and unfinished RT.

We used univariate logistic regression to identify possible risks for unfinished RT. Odds ratios (OR) and 95% confidence intervals (95% CI) for age, gender, presence of some chronic disease as well as the number of chronic diseases per patient are presented in Table 3. Performed univariate analysis has singled out age and gender as significant variables, while presence of chronic disease and the number of it did not reach statistical significance.

**Figure 2.** Distribution of the comorbidities in cancer inpatients infected with COVID-19 who finished and did not finished their radiotherapy.




CLD: Chronic Lung Diseases; CHD: Chronic Heart Disease; DM: Diabetes Mellitus.

**Table 2.** Laboratory findings range distribution before radiotherapy and during incubation or diagnosis of COVID-19.

| Parameters | Before RT | | | During incubation or diagnosis of COVID-19 | | | Pearson Chi-Square | p |
|---|---|---|---|---|---|---|---|---|
| | Normal | Lower | Higher | Normal | Lower | Higher | | |
| RBC | 32 | 17 | 0 | 24 | 25 | 0 | 14.427 | < 0.001 |
| Hb | 26 | 23 | 0 | 20 | 29 | 0 | 13.841 | < 0.001 |
| WBC | 41 | 1 | 7 | 26 | 16 | 7 | 9.156 | 0.057 |
| LYM | 37 | 8 | 4 | 10 | 38 | 1 | 12.189 | 0.016 |
| NEUT | 39 | 3 | 7 | 26 | 14 | 9 | 9.514 | 0.049 |
| PLT | 40 | 7 | 2 | 32 | 16 | 1 | 26.272 | < 0.001 |
| AST | 47 | 0 | 2 | 44 | 2 | 3 | 7.010 | 0.030 |
| ALT | 44 | 0 | 5 | 40 | 1 | 8 | 7.807 | 0.020 |
| Urea | 43 | 0 | 6 | 38 | 0 | 11 | 0.465 | 0.408 |
| Creatinine | 47 | 0 | 2 | 45 | 0 | 4 | 4.868 | 0.158 |

**Table 3.** Univariate binary logistic regression analysis for associations of age, gender, chronic diseases presence and risk for uncompleted radiation therapy.

| Independent variables | OR | 95% CI | P |
|---|---|---|---|
| Age, years | 0.845 | (0.755 - 0.946) | 0.004 |
| Gender | 11.204 | (1.394 - 90.05) | 0.023 |
| Chronic diseases | 0.097 | (0.007 - 1.408) | 0.087 |
| Number of chronic diseases | 0.688 | (0.154 - 3.079) | 0.625 |

## Discussion

To date, there is limited data about the effect of COVID-19 infection in cancer patients on their further oncologic treatment. Cancer is considered a risk factor for severe events and higher mortality rate compared to non-cancer patients [6]. However, cancer patients often have one or more additional comorbidities that are risk factors on their own in terms of the outcome with SARS-CoV-2 infection.

In the study that included 5700 patients with COVID-19 infection, Richardson *et al.* reported hypertension, obesity and diabetes as the most common comorbidities. Authors mentioned that 6% of the observed patients had cancer. The median age of the patients was 63 years, with male predominance with 60.3% of the patients [7]. Processing demographic and clinical characteristic of only cancer patients with COVID-19 infection, Zhang *et al.* reported similar results. Median age of the patients was 65 years and 60.7% patients were men, respectively [8]. It should be born in mind that Zhang *et al.* included 28 cancer patients in their study, while Richardson *et al.* included 5700 COVID-19 patients, but without specific demographic characteristics of cancer patients. Clinical and available demographic characteristic of our patients are similar to ones that can be found in the literature, although diabetes was not listed among the most common chronic medical conditions in our patients, comprising about 6.1%. Moreover, Lippi *et al.* suggested that hypertension could be associated with up to 2.5- fold higher risk of severe events in patients with COVID-19 infection, particularly in elderly patients [9]. Also, El Kassas et al reported that COVID-19 pneumonia is more often in patients with hypertension, diabetes and cardiac disease [10]. However, hypertension represents one of the most common chronic diseases in general, with mean prevalence of 33.4% in men and 32% in women in developing countries and 40.2% in men and 32.2% in women in developed countries [11]. On the other hand, age over 65 years and male gender are related to a possible worse outcome for patients with COVID-19 [12]. One of the possible causes of severe events for male patients with COVID-19 infection may be due to different levels of angiotensin-converting enzyme-2 (ACE2) between men and women and should be further observed [13]. As we did not get all data about severity and complications due to COVID-19 infection in COVID-19 related hospitals of our patients, we obtained data about patients who finished their radiation therapy after COVID-19 infection in the observing period between April and July 2020. More than half of our patients (55.1%) have not completed their radiotherapy in the observing period. From the oncologic aspect, this information is concerning. Often, there is optimum time for adjuvant radiotherapy. Delay of adjuvant or radical radiotherapy may lead to rapid cancer progression. In our study, the age of patients who completed RT was significantly lower compared to patients who did not complete RT after the cured COVID-19 infection. This result may suggest a few things. Older patients are often more exhausted and burdened with cancer symptoms and with pronounced side effects of oncological therapy. Second, due to disease progression or time elapsed since the interrupted radiation, some patients are no longer suitable for radiation therapy. As mentioned before, the age is associated with poor outcome in SARS-CoV-2 infected patients which may result in suspension or interruption of radiotherapy or other oncological treatment modality.

Since the onset of the COVID-19 pandemic, lymphopenia has been singled out as one of the striking laboratory parameters in patients with COVID-19 infection. Guan *et al.* reported lymphopenia in 83.2% of the COVID-19 infected patients, thrombocytopenia in 36.2%, and leucopenia in 33.7%, with emphasis that patients with the severe form of the disease had more noticeable laboratory results such as lymphopenia and leucopenia [14]. Lymphopenia was presented as the most common irregular parameter in the blood count even in COVID-19 infected children [15]. In COVID-19 infected cancer patients, Reale *et al.* notify lymphopenia in 28% of the patients, high level of C-reactive protein in 78% of the patients with decreased platelets in 22% of patients [16]. Decreased lymphocytes was the most common laboratory finding in our patients during the incubation or diagnosis of COVID-19 infection. Nevertheless, comparing range distribution of the lymphocytes before RT and during incubation or diagnosis of COVID-19 there were no significant differences. C-reactive protein was increased in 63.2% of our patients. However, there was no available information for 15 patients. It needs be looked critically at specific oncological profiles of cancer patients as they are often immunocompromised with baseline or treatment induced lymphopenia and increased inflammatory markers with systemic inflammatory response due to underlying cancer disease or the treatment [17-19].

Features of a tumor, tumor localization as well as any applied local or systemic treatment may play a role in susceptibility to SARS-Co-2 virus infection. Head and neck cancers were the most represented group of tumours in our cohort followed by brain tumours and

prostate cancer. In contrast, lung cancer was listed as one of the most reported type of tumour in COVID-19 infected cancer patients [8,16,20]. Patients and disease characteristics such as stage, cancer site and treatment setting in cohort may vary and may be dependent on the department structure as was the case in our study. However, it should not be neglected that patients with head and neck cancers are susceptible to respiratory infections and pulmonary complications, as well as the fact that treatment side effects like chemoradiation may contribute to or increase that risk [21]. Dai *et al.* reported that patients with lung cancer, haematological malignancy and those with metastatic cancer had highest incidence of severe events. Further in their research, authors discussed possible reasons for severe outcomes in haematological malignancies in terms of aberrant lymphocytes and dysfunctional immune response [3]. Earlier in 2009, He at al. observed the impact of severe acute respiratory syndrome (SARS) on peripheral blood lymphocytes [22]. Nevertheless, meta-analysis by Huang *et al.* showed that lymphopenia is the risk factor for bad outcomes in patients with SARS-CoV-2 [23]. Meanwhile, other authors reported that patients with haematological malignancy had twice the mortality rate compared to those with solid cancer [6]. At the point of observation, we did not have any patients with haematological malignancies in our cohort, lung cancer had 8.2% of our patients, while 6% of our patients were in palliative setting.

From the aspects of the therapeutical approach or multimodal approach in cancer patients, Jyotsana *et al.* suggested that patients who are in the setting of active therapeutical setting like chemotherapy, radiotherapy or recent stem cell transplantation are at higher risk of serious manifestations of COVID-19 [24]. In contrast, Lee *et al.* in their prospective cohort study found no significant influence on mortality for patients treated with immunotherapy, radiation therapy, hormonal and targeted therapy in the past 4 weeks prior COVID-19 infection [25]. Also, Dai *et al.* showed that patients on only radiotherapy treatment only did not have significant differences in serious event when compared with non-cancer patients [3]. Indini *et al.* analysed the relationship of COVID-19, immune system and cancer. They hypothesised that cancer patients receiving immunotherapy may experience inadequate immune response in terms of hyperactivation of immune system and possible cytokine storm [4]. In addition, due to the often immunocompromised state in cancer patients, symptoms and signs of COVID-19 could be expected to be different from those in the general population. However, in our cohort, fever was the most prominent symptom followed by cough and tiredness like in general population and patients without cancer [14]. Similar results were obtained by other authors who researched characteristic of COVID-19 cancer patients [3,8]. Tiredness as the symptom is presented as one of the main symptoms of COVID-19. However, determining the origin of fatigue in cancer patients is complex. It should be considered that cancer patients may also experience tiredness as accompanying symptoms of the underlying disease and oncological treatment [26]. Altunisik *et al.* showed that COVID-19 patients may have mucle injury [27]. In this regard, muscle injury may cause muscle fatigue. However, some cancer patients have cancer cachexia with decreased muscle tissue and therefore they can develop early fatigue [28]. In many cases, fatigue is the result of a combination of multiple mechanisms, and consequently may be more prevalent in COVID-19 cancer patients.

## Conclusions

Our results show that COVID-19 cancer inpatients have a similar frequency of symptoms, as well as similar age and gender distribution as the general population with COVID-19. We noticed a statistical significance in terms of anaemia and lower platelets count during the COVID-19 infection, which may reflect different behaviour of COVID-19 cancer patients. Head and neck cancers patients could have more susceptibility to COVID-19 infection than the patients with other tumours. Old age and male gender may be risk factors for the suspension of the radiotherapy in COVID-19 infected cancer patients. Comorbidities did not reach statistical significance as a risk factor for the suspension of the radiotherapy in COVID-19 infected cancer inpatients.

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