

Special aspects of medical care for cancer patients during COVID-19 pandemic

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SUMMARY

The biggest challenge for the World Health Organization today is the fight against the COVID-19 pandemic. The current situation prompted major adjustments in the system of cancer care. In this review, we investigate the aspects of cancer treatment and care during the pandemic, since in this setting oncological services face challenges in determining the feasibility of anticancer treatments while minimizing the risk of infection. Cancer patients are at a higher risk from COVID-19 disease. Therefore, oncological community is discussing on the priorities for providing cancer therapies and care and at the same time minimizing the risk of infection.

Keywords: COVID-19, pandemic, cancer, medical care

INTRODUCTION

Currently, the biggest challenge for Health Systems worldwide is the fight against the COVID-19 pandemic caused by the SARS-CoV-2 virus. Over 80M cases of infection were identified in the world and over 1M in Ukraine for 2019-2020, and the mortality was 1.819.645 and 18.680 cases, respectively (1). The current situation has made major adjustments in the system of cancer care, due to redirection of resources to combat the spread of COVID-19 and for its treatment. This has resulted in changes in the care of cancer patients, namely in reducing screening programs and delaying the diagnosis and treatment of malignant tumors. The oncological services faced the dilemma, which consisted of minimizing the risk of infection while determining the feasibility of anticancer therapy (2, 3). Widespread introduction of telemedicine and outpatient anticancer therapy may partially replace and minimize number of patient's visits to the doctor, but in some cases (surgery, radiation therapy, etc.) this is not possible.

Patients with malignant neoplasms constitute a vulnerable population group during the COVID-19 pandemic due to their suppressed immunity caused by the tumor and/or as a side effect of anticancer therapy. Immunosuppression also increases the risk of opportunistic infections and the development of severe complications requiring treatment in the intensive care unit that can even cause death of a patient (4). Immunotherapy of malignant tumors can cause the development of hyperinflammatory syndromes in patients: acute respiratory distress syndrome (ARDS) and cytokine storm. Due to immunosuppression caused by chemotherapy treatment, oncological patients have an increased susceptibility to coronavirus infection, as well as an increased risk of a complicated course requiring hospitalization in the intensive care unit and mechanical ventilation compared to COVID-19 patients without concomitant oncological pathology (39% versus 8%, $p = 0.0003$) (5).

Social distance and the use of personal protective equipment have not been able to neutralize the risk of COVID-19 infection during hospitalization or hospital treatment. For this reason, the Health Systems began to adjust the procedures for providing cancer care in a pandemic, as well as to reorganize cancer care by investing in telemedicine and other alternatives. For example, strategy of oncological care that envisaged the organization of delivery of antineoplastic agents to the patient's home was created in UK (for example, tyrosine kinase inhibitors or Herceptin for subcutaneous injections). It will allow the patients to avoid the visit of

curative establishment and reduce time of expectation for other patients, creating terms for providing of the social distancing (6). American authors Jindal *et al.* recommended continued adjuvant chemotherapy in hospital settings despite the risk of COVID-19 infection, however, such patients should spend at least 7 days in self-isolation to prevent the prescription of chemotherapy during the incubation period of coronavirus infection (7). Taking into consideration studies showing that patients who received chemotherapy or had surgery one month prior to the detection of COVID-19 have a higher risk of severe clinical course of coronavirus disease compared to patients who did not (75% vs. 43%; OR 5.34; 95% CI 1.80-16.18; $p = 0.0026$), the oncological community is prioritizing on providing cancer care and at the same time minimizing the risk of infection (8).

DIAGNOSIS OF MALIGNANT NEOPLASMS DURING PANDEMIC

In connection with the reallocation of resources during the COVID-19 pandemic, cancer screening was relegated to the background. In the UK screening programs were suspended. Due to the heavy workload of primary care physicians, strict quarantine and patients' apprehension of getting infected COVID-19 in hospitals the early diagnosis of malignant tumors was also negatively affected and created a situation in which patients went to oncological institutions only in the presence of obvious clinical manifestations of malignant tumors - (9). It was also found that reallocation of resources caused a 50% decrease in new patients suspected or diagnosed with a malignant neoplasm, suggesting a decrease in the volume of diagnostic activities. In connection with the COVID-19 pandemic in London 2000 endoscopic examinations, which were planned in patients with suspected gastrointestinal cancer, were postponed. This number corresponds to 120 potential cancer patients (6).

In Slovenia Zadnik *et al.* estimated the number of histopathological and clinical reports of malignancies from two oncology centers in Ljubljana and Maribor. The monthly number of oncology visits by patients was provided from the National Institute for Public Health of Slovenia electronic reference system. Number of mammograms, ultrasounds, CT scans, X-rays and MRI were estimated according to the data provided by Ljubljana Institute of Oncology during the period from November 2019 to May 2020. The results showed a decrease in the number of histopathological and clinical reports by 43% and 29%, respectively. Such data were interpreted by researchers as a decrease in the number of newly

Arch Oncol 2022; 28(1):7-12

Published Online

June 5th, 2021

<https://doi.org/10.2298/A00210205002P>

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Received 2021-02-05

Received in revised form 2021-04-21

Accepted 2021-04-21



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diagnosed cases of malignant neoplasms not equivalent to the absolute number of new reports, and found a decrease of about a third compared to the pre-pandemic period. The largest reduction in screening programs was observed in prostate cancer (75%), bladder cancer (66%) and colorectal cancer (66%). There was also a decrease in primary outpatient visits to surgeons (by 43%) and radiologists (by 19%). The number of diagnostic procedures during this period decreased: mammography by 76%, radiography by 48%, ultrasound by 42%, while the number of MRI and CT scans did not change (10).

In United Kingdom, according to a study by Earnshaw *et al.*, a decrease in referrals for skin cancer by about 50% was observed in April 2020 compared to April 2019 (11).

In Italy, according to a study by Minucci *et al.* the number of referrals for detection of BRCA mutations in March 2020 decreased by 60% compared to January and February 2020 (12).

In a retrospective analysis by Patt *et al.*, the changes in the volume of medical services provided to the US population during the first half of 2020 were estimated using data from the center for processing requests for payment of medical services, which is 5-7% of the Medicare service fee (FFS). Comparison was made of data specific to targeted services related to malignant tumors, namely: screening, outpatient oncologist appointment, surgery and fluid therapy for malignant tumors, for the first 7 months (from January 1 to July 31) 2019 and 2020. The number of procedures was also tracked for each category. In April 2020, at the peak of the US pandemic, screenings for breast, colon, prostate, and lung cancers dropped sharply (by 85%, 75%, 74% and 56%, respectively) compared to 2019. In addition to the screening programs reduction, in 2020 there was a decrease in the number of chemotherapy infusions performed, by 19% in March, by 28% in April, by 30% in May, by 19% in June and by 31% in July compared to the corresponding periods of 2019. In April and June 2020, there was a decrease in the number of biopsies of the breast (by 71% and 31%), colon (by 79% and 33%) and lungs (by 58% and 47%), respectively. Also in this period, a decrease in the number of services provided by doctors was revealed: by 26% in April and by 31% in July. In particular, among these services, the number of mastectomies had been decreasing continuously from April to July, colectomies - in April and May, and prostatectomies in April and July (19).

INFLUENCE OF ANTINEOPLASTIC THERAPY DELAY ON SURVIVAL

The antineoplastic therapy is frequently delayed or even cancelled during the pandemic due to the necessity of minimization of the risk of being infected with the coronavirus SARS-COV-2. This fact can have influence on the prognosis, oncologic disease state and patients' survival. There is limited number of data on COVID-19 disease in patients with malignancies, who are undergoing antineoplastic therapy or are in remission. The results of several investigations show a higher risk of infection, severe course, development of complications of COVID-19 disease and death in patients with malignancies, especially in those who are undergoing the antineoplastic therapy at the moment of infection.

Gupta S. *et al.* studied the effect of clinical factors on the mortality of patients with COVID-19 disease undergoing treatment at intensive care unit in 65 centers in the United States. Among the 2215 patients with

COVID-19 disease included in the research, 112 of them were receiving anticancer treatment. During the follow-up period of 8-28 days (median 16 days) 875 (39.5%) patients died, 1203 (54.6%) were discharged, and 137 (6.2%) continued with the treatment. Out of 112 oncology patients with coronavirus SARS-CoV-2 only 52 (46.4%) recovered, but 60 (53.6%) died. In view of this, anticancer treatment is the factor that is increasing the risk of death (OR 2.15; 95% CI 1.35-3.43) in patients' with COVID-19 (8).

With the purpose to minimize the risk for patients of being infected with SARS-CoV-2, the periods of surgery delay without a significant negative influence on the effectiveness of oncological treatment has become a topical issue. A group of oncologists led by Laura Ardizzone from Memorial Sloan Kettering Hospital (United States) established the list of localizations of malignancies for which the surgery delay has the minimal negative consequences. It included tumors of the brain, breast, colon, stomach, pancreas, liver, bladder, kidneys and lungs. In addition, it could be applied to palliative surgeries, with the purpose to influence the acute pain syndrome that cannot be treated by other (conservative) methods. At the same time the requirements for the patients who have to be primarily hospitalized were determined at the hospital as well as the list of surgeries that could potentially be postponed for several months including in particular prostatectomy, pancreatectomy and, thyroidectomy in case of the absence of adverse factors of tumor prognosis for respective localizations (13,14).

Hartman *et al.* predicted the risk of delaying antineoplastic therapy for 25 localizations of malignant neoplasms depending on the stage and taking into account the concomitant pathology for a period of up to 180 days. In data analysis provided by the Surveillance, Epidemiology, and End Results database (691.854 patients) and by the National Cancer Database (5.436.896 patients), a model of Cumulative Overall Survival and Median Survival was created. This model was integrated into the OncCOVID web application, which has up to 47 parameters and provides an individualized approach to each patient in order to determine the potential treatment delay with minimal risk of reduction of the survival. According to OncCOVID, delayed antineoplastic therapy had minimal adverse effects on the survival of patients with prostate cancer stage II, and the maximum negative effect of delayed therapy on survival in patients with the malignancies of the head and neck of stages I, II and III (15).

A team of investigators from United Kingdom predicted the effect of progressing malignancies on the patients' 5-year survival, number of saved lives and acquired years of life (AYL) in case of surgery delay for 3 and 6 months. Based on the daily risk factors for tumor progression, survival was determined taking into account the age of the patients and the stage of the disease. The analysis was carried out based on data provided by Public Health England National Cancer Registration Service for the period from 2013 to 2017. During one year 94.912 surgeries for solid malignancies were performed in United Kingdom resulting in 80.406 lives saved and 1.717.051 AYL. Based on their predictions surgical treatment delay for 3-months can result in 4.755 additional deaths during one year. while 6-months surgery delay can increase the number of deaths by 10.760 during one year, namely 2.980 additional deaths caused by colorectal cancer, 1.439 caused by lung cancer and 804 caused by breast cancer. Three and six months delay of the surgical treatment for the patients with

malignant tumors can lead to the loss of 92,214 (19%) and 208,275 (43%) AYL, respectively. Therefore, in order to prevent the crisis of the health care system related to the prevention of mortality, the authors insisted on the surgical interventions in patients with malignant tumors in the pre-pandemic order. In addition, they highly recommended eliminating the existing delays in surgical treatments. Most deaths episodes have been reported among lung and breast cancers (17).

An important point was made to evaluate the role of neoadjuvant therapy in terms of delayed surgery. From this perspective, therefore, there are recommendations for the use of endocrine therapy in neoadjuvant mode in cases of estrogen receptor-positive (ER+) breast cancer, not only for the "traditional" prescriptions but also for the safe postponement of surgical treatment (2). The same opinion is shared by American researchers, who believe that if neoadjuvant therapy is possible for some malignant neoplasms, it is advisable to use it as a method of delay with minimal or even zero negative consequences (16).

In the biggest oncological center of India (Tata Memorial Centre, Mumbai) the strategy of providing oncological care has been developed based on an assessment of the potential risks of infection with SARS-CoV-2 by cancer patients at the center. It provided the reduction of the oncological care extent, especially by the avoidance of complex surgeries requiring multiple blood transfusions and prolonged stay at the intensive care unit, the use of hypofractionated radiation therapy, palliative radiation therapy on a single occasion or once a week, reduction of the use of myelosuppressive therapy and the maximum possible crossover to oral systemic treatment (18).

CORONAVIRUS DIAGNOSIS IN CANCER PATIENTS

SARS-CoV-2 diagnosis in cancer patients is crucial for the prevention of the spread of the virus and the potential negative affect of the antineoplastic therapy on its course. Symptoms of COVID-19 in patients with malignancies very often are mild or absent, but cancer patients' mortality from complications of COVID-19 is more than twice as high as in the general population (5.6% vs. 2.3%, respectively) (20). The absence of specific clinical manifestations of COVID-19 in both general population and patients with malignant tumors in particular, create difficulties in infection detection. Often, the clinical course is reduced to typical symptoms: fever, fatigue, general weakness, dry cough, myalgia, shortness of breath, anosmia, ageusia, etc. In some cases, these symptoms may be mild or the course can be even asymptomatic, and some patients may deliberately hide the symptoms of COVID-19 due to their fear of missing treatment. Constant screening for SARS-CoV-2 in cancer patients is required, especially in patients undergoing the antineoplastic therapy (21). In Princess Margaret Cancer Centre in Ontario (Canada) treatment for cancer patients was recommended to be created, in the order of priority: category A - critical patients requiring immediate therapy, category B - patients in need of treatment, but considered uncritical, and category C - generally healthy patients whose treatment may be delayed. In the case of a positive COVID-19 test in patients from category A, it is recommended to provide treatment at a specially equipped area (for patients with COVID-19) or at the chemotherapy department of the day care facility. The treatment of the COVID-19 positive patients from category B should be delayed. The authors recommend detecting SARS-CoV-2 RNA from

the nasopharyngeal mucosa smear by reverse transcription polymerase chain reaction (RT-PCR). For patients whose surgical treatment or radiation therapy is planned, it is recommended to undergo RT-PCR testing 24-48 hours before and then to isolate themselves (22).

Passaro *et al.* recommended considering a possible positive test for COVID-19 in case of cancer of lungs as an episode of individual management. In addition, it was recommended to undergo the basic screening for SARS-CoV-2 for all patients with lung malignancies. In the case of negative test for COVID-19 and the presence of ground-glass opacities on CT, it is recommended to consider the use of bronchoscopy (23).

Cabezón-Gutiérrez *et al.* studied the prevalence of IgG and IgM to SARS-CoV-2 among 229 cancer patients from the University Hospital of Torrejón de Ardoz, Madrid, Spain. The study showed a wide prevalence of seropositive reaction (IgG or IgM) in 31.4% cases (64 positive for IgG and 22 for IgM to SARS-CoV-2), that was higher in patients with pneumonia (OR 7.65; 95% CI 1.85-31.58) (24).

PROVIDING ONCOLOGICAL CARE TO THE PATIENTS WITH COVID-19

Providing oncological care during the COVID-19 pandemic is associated with difficulties. It concerns limiting diagnostic measures, including screening for malignancies, the need to delay or interrupt the antineoplastic therapy in order to reduce the risk of SARS-CoV-2 infection, as well as to finding appropriate and safe treatment of the cancer patients after diagnosis of COVID-19. Given the fact that chemotherapy, radiation therapy and immunotherapy are often accompanied by immunosuppression, most physicians prefer to delay or interrupt their patients' antitumor treatment, which is not always reasonable.

In the study made by Kuderer N. *et al.*, influence of various potential factors, including cancer diagnosis on the prognosis of COVID-19 was evaluated. The study used the data from the COVID-19 and Cancer Consortium (CCC19) databases that included information on 18-years and older patients with confirmed SARS-CoV-2 infection from the United States, Canada and Spain for the period from March 17th to April 16th, 2020. Among 1,035 patients, 928 met the criteria of inclusion to the study. As of May 7th, 2020, 121 (13%) patients died (over a period of 30 days after being diagnosed with COVID-19). An independent factor analysis did not establish a statistically significant connection between recent surgery, medication, and radiotherapy for active malignancies and mortality from COVID-19 over a 30-day period. The only factors that influenced on the worsening of the prognosis of COVID-19 were the age of the patients and the presence of concomitant pathology. After adjusting the multivariate model, the investigators found out an increased risk of death over a period of 30 days after diagnosis of COVID-19 in patients with active malignancies (progression versus remission OR 5.20; 95% CI 2.77-9.77). This gives a reasonable conclusion that antineoplastic therapy should be continued during the pandemic. However, the authors recommend considering the results as a basis for further studies of the influence of anticancer treatment on the course of COVID-19 (25) (Table 1).

Zhang *et al.*, in their retrospective incidence study evaluated medical data from 28 cancer patients positive for SARS-CoV-2 infection. These patients underwent treatment at the Intensive Care Units of three hospitals in Wuhan (China) during the period from January 13th 2020 to February

26th, 2020. The most common form of malignancy was lung cancer (25%) with the mortality of 28.6%. In the cases when the antineoplastic therapy was administered 14 days before the diagnosis of COVID-19 disease, there was an increased risk of severe course of COVID-19 and complications, namely administration to the intensive care unit followed by mechanical ventilation (hazard ratio, HR 4.079; 95% CI 1.086-15.322; P = 0.037). The results of this study revealed that antineoplastic therapy administered 14 days before COVID-19 diagnosis should be considered as a factor leading to a severe clinical course of SARS-CoV-2 infection. This study also showed that symptoms of COVID-19 in cancer patients were identical to ones in the general population, except for anemia and hypoproteinemia which are accompanied by a worse clinical course. Therefore, patients with malignancies receiving antineoplastic therapy should be tested before the treatment and reduce the risk of SARS-CoV-2 infection during the first 14 days after treatment in order prevent the development of severe COVID-19 course (26) (Table 1).

Liu *et al.* in their multicenter incidence study included data from 641 patients with COVID-19 from the fourteen hospitals of Wuhan (China).

Among 641 patients 105 (16.4%) were cancer patients and 536 (83.6%) were patients without cancer. The results of the study showed that the patients with malignancies had a higher risk of severe complications and death from COVID-19, especially patients with hemoblastosis, lung cancer and metastatic cancers. The study also revealed that patients who received medical treatment or surgery within 40 days before the first symptoms of coronavirus infection had a worse course, often accompanied by the need for mechanical ventilation, and had an increased mortality. The only anticancer therapy with no statistically significant connection with COVID-19 disease was the radiation therapy (27) (Table 1).

However, there are also studies that do not confirm the influence of the antineoplastic therapy on the risk of complications or mortality caused by COVID-19 disease. Lee *et al.* made a prospective observational study including data from 800 cancer patients with laboratory-confirmed SARS-CoV-2 infection from 55 UK Cancer Centers. These data were entered into the UK Coronavirus Cancer Monitoring Project (UKCCMP) Register for a period from March 18th to April 26th, 2020. The results of this study showed that the mortality rate among patients who received

Country	Number of patients	The presence of concomitant pathology ¹	Average age of patients	Localization (percent) of malignancy	Observation period (days)	Mortality	Malignant neoplasm status (percent) ²	The most common symptoms	Received anti-Covid-19 treatment (percent)	Received antitumor treatment (percent) ³	Surgical treatment ⁴	Cause of death	Reference
USA	928	+	66	Breast cancer (20.6%), prostate (16.4%) hematological malignancies (22%)	30	13%	Remission (45.5%), active cancer (42.7%)	Asymptomatic course (40%), cough, shortness of breath, fever	Hydroxychloroquine (10%), azithromycin (10%), combination of these drugs (20%)	Cytotoxic therapy (39%)	19%	N.D.	(25)
China	28 (10 patients with Stage IV cancer)	+(diabetes cardiovascular diseases)	65	Cancer of the lungs, esophagus, breast	-	28.6%	-	Fever, dry cough, fatigue	Antiviral drugs ribavirin and ganciclovir (71.4%), antibiotics (82.1%), corticosteroids (53.6%), intravenous immunoglobulin (35.7%)	Chemotherapy/ immunotherapy/ radiation, targeted/ combination therapy (21.4%)	N.C.	Pulmonary embolism, ARDS, septic shock, acute myocardial infarction	(26)
UK	800	+(diabetes cardiovascular diseases, COPD)	69	Cancer of the gastrointestinal tract, breast, lungs	38	28%	Active cancer (50% were metastatic)	Fever, cough, shortness of breath	N.C.	Chemotherapy (35%)	4%	N.D.	(28)
China	105	+(diabetes cardiovascular diseases, COPD)	64	Cancer of the gastrointestinal tract, breast, lungs	55	11.43%	Active cancer (including metastatic)	Fever, dry cough, fatigue	Antiviral (77.1%), antibiotics (71.5%), systemic glucocorticoids – (18.1%)	Chemotherapy (14.1%), radiation therapy (12.2%), targeted therapy (3.8%), immunotherapy (5.7%)*	7.6%*	N.D.	(27)
Germany	39	+	66	Lung cancer, urogenital malignancies, breast	44	20.5%	Active cancer (including metastatic)	N.D.	Antibiotics (64%), hydroxychloroquine (10%), hydroxychloroquine + lopinavir (30.7%)	Chemotherapy / immunotherapy / radiation therapy (36%)	12.8%**	Hypoxia, ARDS, sepsis	(31)

1 in relation to Covid-19 as factor complicating the course of the disease

2 remission or active cancer

3 four weeks after Covid-19 diagnosis

4 for a period of four weeks after Covid-19 diagnosis

* for a period of 40 days

** four weeks prior to Covid-19 diagnosis

ARDS – acute respiratory distress syndrome, COPD– chronic obstructive pulmonary disease, N.C.- not conducted, N.D. – not detected

Table 1. Influence of antineoplastic therapy delay on survival

chemotherapy within 4 weeks after receiving a positive COVID-19 test did not differ from that of patients who did not receive chemotherapy, with 27% and 29% rates, respectively. After adjusting data by age, comorbidity, sex, and localization of the primary tumor, it was found that chemotherapy (adjuvant or palliative) administered within 4 weeks after the diagnosis of COVID-19 was not considered a risk factor worsening clinical and pathogenetic episodes or a trigger for mortality caused by coronavirus infection. A similar relationship was observed in patients receiving radiation, targeted, immunotherapy, or surgical treatment over this particular period suggesting that delaying surgery is not a rational solution in this case (28) (Table 1).

Despite the fact that the cancer patients are immunosuppressed due to antineoplastic therapy and have increased risk of severe complications, in most cases their COVID-19 treatment does not differ from that in people without malignancies and involves symptomatic therapy (29).

From March 13th, 2020 to April 25th, 2020, the researchers at the Curie Institute, Paris (France) recorded all detected cases of COVID-19 in patients with breast cancer. Among 15.600 patients treated within four months, 59 were COVID-19 positive. The study showed that the mortality rate was 7% (four patients out of 59; two with metastatic breast cancer, one on adjuvant endocrine therapy, one on neoadjuvant chemotherapy) and that was not associated with breast cancer. Risk factors for severe complications and death from COVID-19 for breast cancer patients in this study were identical to the ones in general population, namely, age over 70 years and hypertension (30).

INTERPRETATION

The COVID-19 pandemic has become a real challenge for medical care in general, and especially for cancer care. The problem of higher susceptibility of cancer patients to coronavirus SARS-CoV-2 raises doubts and discussions about the priority of diagnostic and therapeutic measures. The research made by scientists creating strategies for cancer therapy depending on the status of the malignant neoplasm, play the role in normative documents, which oncologists use as their guides. The telemedicine can partially reduce the frequency of hospital visits, but in cases where the face-to-face encounter with a patient is necessary it is not always possible to avoid infection. Taking into account the studies showing greater susceptibility of cancer patients to COVID-19, delaying the antineoplastic therapy may be justified. However, it is necessary to consider all the risks of such delay and employ individualized approach to patients taking into account the localization of the malignancy and the possible maximum delay without affecting the survival of patients. A number of scientific studies have shown that delaying surgical treatment cannot be a rational method of reducing the risk of SARS-CoV-2 infection. So, in cases where radical surgery is possible, it is recommended to use it or instead use the neoadjuvant chemotherapy / hormone therapy as an element of delay.

Is presence of a malignancy a factor that is worsening the prognosis of COVID-19 disease? There is no definite answer to this question, but most studies indicate that patients who receive anticancer treatment have increased mortality that arise from complications associated with COVID-19 disease compared to patients in remission. Since there are currently no large-scale studies on the features of the cancer patients with

COVID-19 treatments, a definitive recommendation cannot be formulated. However, most scientific studies are inclined to believe that after getting a positive test for COVID-19 the antineoplastic therapy should be continued. Therefore, the COVID-19 pandemic has led to a number of serious issues, the rational solution of which can be achieved by conducting prospective research involving a large number of patients and taking into account the localization of the malignancy, the presence of the antineoplastic therapy, comorbidities and age.

Declaration of Interests

Authors declare no conflicts of interest.

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