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Review Article

COVID-19 and the Severity of the Disease in Different Types of Cancer

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Abstract

Italy, Spain and the USA suffered the most in the early stages of the world wide outbreak of COVID-19 and subsequently the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic on 12 March 2020. Cancer patients with comorbidities (hypertension, diabetes and cardiorenovascular diseases) can lead to severe illness and death as cancer patients have a higher risk of severe illness and death than COVID-19 patients without cancer. Severe COVID-19 reflects dysregulated inflammation and it has been repeatedly shown that inflammation could produce a hypercoagulable state in cancer patients. Cancer patients that obtain COVID19 are treated according to the appropriate symptoms and oxygen therapy. Cancer patients that are prior cancer therapy, receiving therapy and post therapy are treated differently for the control of the progression of their cancers as well as the possibility of obtaining COVID-19. Cancer patients under active oncological therapy as well as those who received antitumor therapy within 14 days before diagnosis are at elevated risk for severe complications and show a higher mortality rate due to COVID-19. A higher proportion of severe COVID-19 was also connected to immune checkpoint inhibitor treatments. It is reported that COVID-19 positive patients that had surgery are likely to be at higher risk of clinically severe events than those who did not have surgery. Postponing certain cancer surgeries may be associated with increased risk of progression; although the impact of surgical waiting times for different cancers may vary. For patients that already started with

radiotherapy, finishing treatment is a priority, either following initial planned fractionation schedules or after planned recalculation to shorten treatment duration. For patients who have not started radiotherapy yet, other treatment options must be investigated. Cancer patients receiving active chemotherapy treatment may be at greatest risk of both COVID-19 infection and severity due to increased immunosuppression. The clinical outcomes of patients with hematological malignancies were worse, with a mortality rate twice that of patients with solid tumors, in a comparative study. Hematological malignancies, such as leukemia and lymphoma, can affect the immune system directly. The best treatment for solid cancers during the pandemic depends on the cancer type.

Abbreviations

ACEIs	angiotensin-converting enzyme inhibitors
ADT	Androgen deprivation therapy
ARBs	angiotensin-receptor blockers
ARDS	acute respiratory distress syndrome
BTK	Bruton's tyrosine kinase
CLL	Chronic lymphocytic leukemia
CRP	C-reactive protein
DCIS	Ductal carcinoma in situ
EMN	European Myeloma Network
ERA	Endothelin receptor antagonists
EUBREAST	European Breast Cancer Research Association of Surgical Trialists
HCC	Hepatocellular carcinoma
HL	Hodgkin lymphoma
ICI	immune checkpoint inhibitors
IL-6	Interleukin-6
mCRPC	Metastatic castration-resistant prostrate cancer ()
MM	Multiple myeloma
PCT	Procalcitonin
PD-1	Programmed death 1
RCC	Renal cell carcinoma
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
TERAVOLT	Thoracic Cancers International COVID-19 Collaboration
VTE	Venous thromboembolism
WHO	World Health Organization

Introduction

The SARS-CoV-2 outbreak (sixteen years after the SARS-CoV-1 outbreak) started in December 2019 in Wuhan in the Hubei province of China. People from other provinces in China as well as from around the world became infected soon after the initial outbreak. Among the initially affected countries, Italy, Spain and the USA obtained the most infections. The World Health Organization (WHO) declared the COVID-19

outbreak a global pandemic on 12 March 2020 due to its worldwide occurrence. At the start of November 2020, the USA had the most infections, followed by India and Brazil, while a second wave of infections took place in Europe. COVID-19 is an extremely transferrable disease and can spread rapidly with an incubation period of 5-6 days on average, although it can take as long as fourteen days. Clinically it appears in different severities in infected persons that can even be life threatening.

The symptoms and diagnosis of COVID-19 in persons having cancer. The most common symptoms of COVID-19 are: fever, dry cough and tiredness. Less common symptoms are: aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on skin, or discoloration of fingers or toes. These symptoms can be the same as observed in the cancer patients. These similarities may make it difficult to detect COVID-19 in cancer patients or detection is at a more advanced stage of COVID-19. The COVID-19-specific Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) test is used for detection when there is a possibility of infection. Testing for other common respiratory viruses can also be done at the same time if the corresponding symptoms are observed. Cancer patients with the following risk factors must be monitored closely: older age, frailty, disability, immunosuppression, generalized systemic inflammation as well as multiple comorbidities. These comorbidities are existing chronic diseases that could put people at a higher risk of developing complications if they are infected with the Coronavirus. These factors can lead to severe illness and death as cancer patients have a higher risk of severe illness and death than COVID-19 patients without cancer [1-5].

This review article will focus on the severity of COVID-19 on cancer patients in general, the different types of cancer treatments in general and on specific types of cancer. Distinction will be made between hematological malignancies (chronic lymphocytic leukemia and multiple myeloma) and solid tumors (head and neck cancers, oral cancer, thoracic cancer, cancer of the lung, breast, prostate and kidney, colorectal cancer and liver cancer).

COVID-19 Symptoms and Severity

Cancer patients with COVID-19 produced increased levels of products that increase the severity of the COVID-19 illness like products that increases the risk of coagulation of blood. Noticeable increased D-dimer levels had been observed in cancer patients having COVID-19 leading to hypercoagulability that were linked to the severity and mortality rate of the disease. The D-dimer levels in cancer patients were also significantly higher than in patients without cancer and can be used for the diagnosis of COVID-19 in cancer patients. Hypercoagulability is caused by inflammation in severe COVID-19 cases. High procalcitonin (PCT) and interleukin (IL)-6 levels are associated with severe and critical illness and linked to higher D-dimer levels. Cytokines and inflammatory mediators trigger damage in endothelial cells of pulmonary and peripheral blood vessels due to COVID-19 and activate the coagulation and fibrinolysis systems [6,7].

The Memorial Sloan Kettering Cancer Centre diagnosed 423 patients from a total of 2 035 cancer patients with symptoms of COVID-19. Fever (78%) and cough (82%) were the most shared symptoms observed, while shortness of breath (44%) and diarrhea (26%) had a lower appearance. Forty percent of the COVID-19 patients were hospitalized, 20% developed severe respiratory illness (90% were placed on ventilators) and 12% died within 30 days. Factors that lead to hospitalization and severe disease were: age older than 65 years

and treatment with immune checkpoint inhibitors (ICIs), while chemotherapy treatment and major surgery had no effect [8].

Treatment of Cancer Patients with COVID-19

Cancer patients that obtain COVID-19 are treated according to the appropriate symptoms and oxygen therapy. Oxygen therapy is the most common treatment for COVID-19. Patients with comorbidities (hypertension, diabetes and cardiorenovascular diseases) are given renin angiotensin system blockers, such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) treatment. These treatments lead to elevated ACE2 concentrations that can reduce the infection rate in cancer patients or the mortality rate linked to acute respiratory distress syndrome (ARDS) [1,7].

Cancer patients that are prior anticancer therapy, receiving therapy and post therapy are treated differently with the main goal of preventing infection with COVID-19. Prior to start of therapy: Single agent therapy or keeping cancer-directed therapy for patients >65 years old and patients at any age with a significant comorbidity (diabetes mellitus, chronic lung disease and cardiovascular disease). The comorbidities can lead to a higher incidence of severe COVID-19 in cancer patients. In a case study it was reported that persons older than 85 years had the highest mortality (10% - 27%), followed by persons between 65-84 years (3% - 11% mortality), followed by persons between 55-64 years (1% - 3%), followed by persons between 20 - 54 years (<1%) and finally persons ≤19 (small number of mortalities as shown in other case studies). Contact with high risk areas of getting infections must be avoided by using telemedicine for patient assessment, patients must be advanced to treatment centers without getting in contact with COVID-19 or related diseases. Make use of laboratories closest to the patient's homes for collection of blood for cancer testing. Post therapy: Postpone any imaging throughout or after treatment has ended for clinical analysis when the chances of obtaining COVID-19 is low, except if it is crucial for medical intervention or continued care. The patients must be informed of the risks of the planned treatment and alternative treatments as well as consultation methods available [7,9].

The Effect of COVID-19 on the Three Major Treatment Methods: Surgery, Radiotherapy, Chemotherapy

Cancer patients under active oncological therapy as well as who received anti-tumor therapy within two weeks before diagnosed for COVID-19 are at a higher risk for severe illness and with a higher mortality rate [10-12]. Surgery increases the risk of severe illness, while radiotherapy doesn't have any effect in comparison to non-cancer patients [13]. In a combined study of the records of Zhongnan Hospital of Wuhan University and the Tongji Hospital of Huazhong University of Science and Technology, both in Hubei, China, a higher proportion of severe COVID-19 was connected to ICI (immune checkpoint inhibitors). They observed a higher non-significant proportion of severe COVID-19 in cancer patients who received ≥3 cycles of ICI (immune checkpoint inhibitors). ICI exposure may worsen COVID-19 severity and is associated with hyper activation of T-cells, leading to additional harm to the respiratory epithelium. A high ratio (63.63%) of cancer patients, who received ICI prior to COVID-19 diagnosis, developed severe COVID-19 illness. The onset of COVID-19 severity and mortality may be associated with the duration of exposure to ICI. Restoration of immunocompetence with ICIs influences cytokine release syndrome development and adds to COVID-19 severity and ARDS [14,15].

Certain anti-tumor therapy may have a positive COVID-19 outcome. Five patients who had Waldenström macroglobulinemia were treated with the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib after obtaining lung inflammation and hypoxia as a result of COVID-19. Other groups also stated the potential protective effect of acalabrutinib in patients with lymphoproliferative disorders affected by severe forms of COVID-19 and are now busy with clinical trials. BTK inhibitors are improving hypoxia in patients with severe COVID-19 by mediating an inhibition of exaggerated monocyte autophosphorylation and reduction in interleukin (IL)-6 production [2].

Surgery

It is reported that COVID-19 positive patients that had surgery are likely to be at a higher risk of clinically severe events than those who did not have surgery. Thus, protective measures must be reinforced and the visits of cancer patients to the hospital limited. Cancer patients must be screened before an operation and those with a high risk of obtaining COVID-19 must be tested. There is a need for working with the hospital to ensure that adequate supplies (PPE, staffing, and bed capacity) will be available for nonselective, time-sensitive surgeries. Surgery in the time period of COVID-19 that must be prioritized are when there are higher chances of cure (primary, neoadjuvant or recurrent settings) and when there are no effective non-surgical treatment options or when the best non-surgical treatments were not effective [16-19].

Postponing certain cancer surgeries may be linked to increased risk of advancement and therefore the tumor doubling time must also be taken into consideration. The impact of surgical waiting times for different cancers may vary. Delayed oncologic surgeries may result in tumors that are no longer resectable, ending in a lower survival rate. Three categories can be distinguished according to the rate of cancer development: high risk (preferably no delay in surgery), intermediate risk (surgery can be postponed for up to 3 months) or low risk (surgery can be postponed for more than 3 months). Three to four weeks delay in about 48% of the major cancers and an additional 2-4 weeks delay for nearly 76% of the cancers following the completion of neoadjuvant treatments were proposed by research groups [16-19].

Radiotherapy

Radiotherapy can be divided into primary and palliative radiotherapy. The priority of radiotherapy can be divided into three sections. Priority one includes: primary radiotherapy for diseases in which the efficacy of radiation therapy is proven and the speed of disease progression is not slow, such as head and neck cancer, esophageal cancer, lung cancer and uterine cervical cancer as well as palliative radiotherapy for alleviation of spinal cord compression, bleeding from the tumor or symptomatic brain metastasis. Priority two includes: primary radiotherapy for rare cancers such as sarcoma, neuroendocrine tumor and malignant as well as palliative radiotherapy for painful bone metastasis that cannot be controlled by drugs and suprarenal cava syndrome for which stent is not indicated melanoma. Priority three includes: primary radiotherapy for brain tumors, pancreatic cancer and malignant lymphoma. Workforce management and planning for safety of patients and staff as well as wellbeing management must be prioritized [20-21].

For patients that already started with radiotherapy, finishing treatment is a priority, either following initial planned fractionation schedules or after planned recalculation to shorten treatment duration. For the weekly

visits, telemedicine and phone calls could be advocated to limit the time spent in the hospital every day. For COVID-19 positive patients, dedicated areas, separate exit/entrance and dedicated time slots have to be planned. For patients who have not started radiotherapy yet, priorities should be also fixed as per tumor sites, adjuvant or neoadjuvant settings and the possibility of delaying irradiation in settings where primary chemotherapy or endocrine therapy could be administrated [17,22].

Chemotherapy

Cancer patients receiving active chemotherapy treatment may be at greatest risk due to increased immunosuppression, although other studies' findings suggest that cytotoxic chemotherapy, immunotherapy, hormonal therapy and targeted therapy have no effect on the mortality due to COVID-19 [23]. The higher susceptibility to COVID-19 is to a degree owing to the cancer, leading to a chronic immunosuppressive state as well as chemotherapy that may also effect the complications due to COVID-19. An infection could have direct (severity or mortality) and indirect (cancer treatment delays or hospitalizations that can have a negative effect on effectivity of therapy and even result in mortality) prognostic consequences [24-27,11]. Children receiving anticancer chemotherapy, on the other hand, may have a mild or asymptomatic progression of COVID-19, although a more severe progression can't be excluded. The preventive measures should not cause postponements or obstacles in oncological treatment of children [27].

Several measures have been taken to reduce the risk of obtaining COVID-19 by cancer patients under chemotherapy: (1) changing to medications that patients can buy at their local pharmacies, (2) changing to regimens with the same effectiveness, but reduce the number of visits to the chemotherapy centers, (3) changing to regimens where treatment can be stopped and continued after a delay dependent on the progression of the cancer, (4) increasing the concentration of medication that decrease the number of visits, (5) using different formulations of the same drug, with different pharmacokinetics, that reduces the number of visits or the time duration at chemotherapy centers, (6) changing from short acting to long acting medication and (7) changing to medication requiring single administration over multiple administrations [28].

The Clinical Impact of COVID-19 on Different Types of Cancer

Different cancers have different susceptibilities to COVID-19 as well as severity of COVID-19. Among cancer patients, there is a higher incidence of both respiratory failure (54%) and ARDS (38%) than previously reported, being respiratory failure more frequent in those patients with previous anemia as well as among subjects with bilateral infiltrates (79%) [10]. Venous thromboembolism (VTE) represents a highly frequent complication in cancer patients with SARS-CoV-2 infection with an overall rate of newly diagnosed VTE of 14% and a recurrence rate of 15% among previously diagnosed in the study. Even more concerning is that up to 20% of patients under chronic anticoagulation therapy a new VTE was found. Thus, presence of bilateral pneumonia, severe neutropenia, previous history of VTE or pulmonary tumor involvement should be considered in evaluation of COVID-19 cancer patients [10-11].

In a study of 3 232 patients with pathogen-confirmed COVID-19 who were hospitalized at Tongji Hospital in Wuhan, China, differences between hematological and solid tumor cancers were observed. The COVID-19

development in patients with hematological malignancies were more severe, with a dying rate twice that of patients with solid tumors (50% vs. 26.1%). The dying rate of cancer patients with COVID-19 was 26.4%, which was significantly higher than that in the non-cancer population. Hematological malignancies (leukemia and lymphoma) have a direct influence on the immune system with T cell senescence and exhaustion as main characteristics involved in immune dysfunction. Cancer patients who were diagnosed with cancer within 10 years have a larger risk of dying than those who had survived cancer for more than 10 years. The higher risk is due to: (1) after-effects of surgery and the immunosuppressive effects of antitumor therapy, (2) biological characteristics of the tumor itself and (3) inflammatory reaction in the tumor microenvironment. The number of complications (acute respiratory distress syndrome, myocardial injury, arrhythmia, kidney injury, secondary infection and shock) contribute to the mortality outcome in cancer patients. Two or more complications had a significantly higher risk in COVID-19 severity [11,24,29].

Hematological Malignancies

Cancer patients with hematological malignancies must be treated with the same precautions as mentioned in the treatment methods to reduce the risk of obtaining COVID-19. The possibility of interactions between cancer and COVID-19 therapy must be taken into consideration [30-32].

When cancer patients with hematological malignancies obtained COVID-19 the following was observed: (1) treating patients with severe COVID-19 with azithromycin or low dose corticosteroids was linked to a lower death rate, (2) comorbidities that have an added risk for mortality is: age over seventy year's old, uncontrolled hematological malignancy, neutropenia and a C-reactive protein (CRP) and (3) autologous or allogeneic stem cell transplantation patients displayed lower mortality rates than patients not receiving any stem cell transplantation [32].

The effect of COVID-19 was obtained for Chronic lymphocytic leukemia (CLL), Hodgkin lymphoma (HL) and Multiple myeloma (MM).

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia is the most common type of leukemia in the western world. Lymphoma patients are considered as immunocompromised and different treatments can have a positive or negative effect on the susceptibility and severity of COVID-19. Patients with lymphoma must be tested for COVID-19 before starting with anti-cancer therapy and telemedicine/virtual visits must be considered if possible. A joint study by ERIC, the European Research Initiative on CLL, and CLL Campus was carried out on 190 patients with CLL and confirmed COVID-19. Their conclusion was that: (1) COVID-19 severity increases with age; (2) antileukemic treatment (particularly BTK inhibitors) appears to have a protective effect; (3) age and comorbidities did not impact on mortality, suggesting a large role played by CLL and immunodeficiency. A different study group observed an increased rate of COVID-19 infections as well as increased hospitalization in patients treated with venetoclax-based combinations and chemo-immunotherapy as primary treatment, while another group claimed that ibrutinib reduces the risk of obtaining COVID-19 [32-35].

Recommendations of the American Society for Hematology in caring for CLL patients: (1) outpatients with COVID-19 must carry on with their treatment, (2) treatment modification of CLL patients with more

severe COVID-19 depends on the aggressiveness of the CLL and increase in the severity of COVID-19 complications, (3) decisions on continuation or discontinuation of treatment must be considered on a patient by patient basis, (4) monoclonal antibody treatment must be placed on hold and (5) if the patient is receiving a B-cell receptor signaling inhibitor, discontinuation of the treatment for a short while and resumption thereafter can have a beneficial effect in overcoming COVID-19 symptoms [36].

Hodgkin Lymphoma (HL)

Hodgkin lymphoma is a very curable cancer with a high success rate (80%-95%). It is advisable to test for COVID-19 before the start of anti-cancer treatment. Chemotherapy, combined modality therapy and radiation therapy is advised when patients are negative for COVID-19 and the emphasis must be placed on reducing the visits to cancer treatment centers [31].

Multiple myeloma (MM)

Multiple myeloma (MM) is the most common leukemia in the USA with more than 130 000 cases. The severity of COVID-19 in MM patients varies drastically. COVID-19 positive MM patients with mild symptoms can be treated as outpatients. Age and cardiovascular risk factors were linked to MM patients admitted to hospital, while severe hypogammaglobinemia, statin use, elevated D-dimer, CRP or ferritin were linked to mortality. Anti-SARS-CoV-2 antibodies developed in patients that cleared infection. The onset of dyspnea followed by ARDS (20% of cases) was a significant complication in patients with severe disease. Mechanical ventilation was needed in 12.3% of patients. Other complications have included arrhythmias, acute cardiac injury and shock. Out of 21 critically ill patients admitted to the ICU in the United States, one-third developed cardiomyopathy [37,38].

The European Myeloma Network (EMN) and ABHH Monoclonal Gammopathies Committe made recommendations concerning the treatment of MM patients with COVID-19: (1) treatment should be administered in cases where acute renal failure, extended bone disease, heavy anemia, or other aggressive myeloma features are present, (2) if anti-myeloma treatment has been started, this might continue for patients with an asymptomatic COVID-19 infection and active myeloma, (3) anti-myeloma treatment must stop when COVID-19 symptoms are present, (4) patients with MM and COVID-19 infection can receive novel and investigational agents against SARS-CoV-2, (5) drugs that are used for SARS-CoV-2 treatment, medication for treatment of comorbidities and drugs for anti-myeloma treatment may have significant interactions with other drugs and may result in significant hepatic, cardiac or renal toxicity, (6) autologous stem cell transplant must be delayed for three months or a minimum of 21 days if the stem cell transplant is a priority [39,40].

Older aged MM patients need extra measures to control the risk of getting infected by COVID-19. If they are infected, the severity of the COVID-19 symptoms will determine what will be the best strategy for MM and COVID-19 treatment [41].

Solid Tumors

The best treatment for solid cancers during the pandemic depends on the cancer type. Risks must be

evaluated in connection with what therapy was the traditional, exclusive standard of care, what alternatives are there and whether combinations of different therapies will reduce the risk of obtaining COVID-19 and the severity of it.

Head and Neck Cancers

Head and neck cancers are complex and difficult to manage, leading to postponements that makes treatment more challenging. Surgery is the main treatment of head and neck cancers. The following aspects are important in deciding whether to operate or not: (1) testing for COVID-19 infection, (2) hospital wards and intensive care units availability, (3) the rate of increase in cancer patients, (4) the degree of urgency, (5) the difficulty of the surgery and (6) the risk of contaminating the caregivers (tracheotomy) [17,42].

Alternative treatments must be evaluated for COVID-19 risk management. All indications for combined chemoradiotherapy must be maintained, as well as the usual delays between diagnosis and radiotherapy (≤4 weeks) or between surgery and radiotherapy (6-8 weeks). Fractionation must be optimized: favor hypofractionation (early stage larynx, elderly or comorbid patients). Where surgery is the traditional, exclusive standard of care, head and neck oncologists should evaluate the magnified, COVID-19-specific multilevel risks of surgery and risks of alternative therapies in the context of multidisciplinary discussion and shared decision-making [17,43].

Head and neck cancer treatment in COVID-19 positive patients. The surgery must be delayed in old age patients and patients with comorbidities (cardiovascular disease and hypertension). Surgery must be done in the following way: (1) on an emergency basis only, (2) in dedicated operating rooms (3) by only essential personnel. Radiotherapy must be managed in the following way: (1) delayed if patients are found positive for COVID-19 before starting with treatment, (2) the treatment in patients with mild symptoms must be continued in patients that became COVID-19 positive during treatment and (3) treatment must be discontinued and delayed in patients with severe COVID-19 complications [42,44] .

Oral Cancer

Oral cancer includes cancers of the lips, tongue, cheeks, floor of the mouth, hard and soft palate, sinuses and pharynx (throat). Squamous cell carcinoma are clinically advanced when they are normally diagnosed, leading to high mortality and morbidity that can increase due to lockdown restrictions due to COVID-19 [45].

Many factors have been identified that make oral cancer patients high risk candidates for COVID-19 infection and severity of the disease: (1) increased protease levels in chronic periodontitis and oral cancer may be associated with an oral mucosa mediated SARS-corona virus-2 infection, (2) low melatonin (anti-inflammatory, antioxidant properties) levels, (3) melatonin can upset the cathepsin mediated fusion of SARS-corona virus-2 and host cell that reduces the susceptibility, (4) over expression of Furin will increase more conversion of S protein of the virus particle, (5) overexpressed ACE2 will bind to the S protein on a larger scale, (6) oral cancer patients are more prone to SARS CoV2 reinfection leading to viremia, (7) oral comorbidities such as oral squamous cell carcinoma and oral potentially malignant disorders in terms of EMMPRIN overexpression as a target for SARS-CoV-2, increases the susceptibility [46-48].

Thoracic Cancers

Thoracic patients with COVID-19 symptoms must be screened for active COVID-19, especially if there is a suspicious CT-scan. Lymphopenia may be a result of advanced COVID-19. Active anticancer treatment must be stopped if a suspected or confirmed diagnosis of COVID-19 is present. Chemotherapy or surgery 14 days before the appearance of symptoms may increase the risk of severe complications. Anti-cancer treatment can commence again when the patient has completely recovered from COVID-19 [49].

Two hundred patients from the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry from eight countries were used in a study to determine the major factors causing death due to COVID-19. Cancer patients included in the study met the following requirements: (1) the presence of any thoracic cancer (non-small-cell lung cancer [NSCLC], small-cell lung cancer, mesothelioma, thymic epithelial tumors, and other pulmonary neuroendocrine neoplasms) (2) a COVID-19 diagnosis, either laboratory confirmed with RT-PCR, suspected with symptoms and contacts, or radiologically suspected cases with lung imaging features consistent with COVID-19 pneumonia and symptoms. The patients were grouped according to specific criteria: (1) current or former smokers, (2) had non-small-cell lung cancer, (3) were on therapy at the time of COVID-19 diagnosis and (4) on first-line treatment. Only smoking history was associated with increased risk of death in a multivariable analysis [50].

Lung Cancer

Lung cancer is the most common solid tumor cancer found in patients with COVID-19 and the effects of Covid-19 can be decreased lung volume along with pneumonia with severe complications. The death rate in lung cancer patients due to COVID is higher than in COVID-19 patients without cancer. Overexpression of ACE2 in lung cancer patients can lead to a higher risk of getting infected by COVID-19 [10-11,51-58].

Many studies were done on the severity of COVID-19 in lung cancer patients. A study done by the Memorial Sloan Kettering Cancer Center, New York, USA found that COVID-19 was severe in patients with lung cancer, but had a minor effect on the death rate. Smoking status and chronic obstructive pulmonary disease determined the severity of COVID-19, while cancer treatment had no effect on the severity [51]. In non-small-cell lung cancer there is an increased risk for patients older than 60 years to have severe complications [52]. A study of patients with lung cancer treated with programmed death 1 (PD-1) blockade therapy indicated that there were no effect on COVID-19 severity [52]. Other studies on cancer treatments indicated that different treatments had different effects on COVID-19 severity and death rate: last anti-tumor treatment within 14 days, including chemotherapy, radiotherapy, targeted therapy and immunotherapy combined with chemotherapy had a more severe effect [53,54].

Different substances were tested for COVID-19 treatment in lung cancer treatments. In one study, hydroxychloroquine and azithromycin combined were found to have a positive effect [55].

Anti-tumor treatment should only be given to patients who are already undergoing therapy. The initiation of radiation therapy in new patients should be discussed in the frame of multidisciplinary board meetings [17].

Breast Cancer

Breast cancer patients with comordities had an increased risk of COVID-19 complications and death. The Institut Curie hospitals linked hypertension and age over seventy years to a greater risk of admittance to intensive care units and/or death [59]. More than one comorbidities have a greater impact on the death rate of COVID-19 positive breast cancer patients [60].

Specific treatments were shown to increase the risk of obtaining COVID-19 and therefore protocols were set up to decrease the risk of breast cancer patients in obtaining COVID-19. A combined international survey of the European Breast Cancer Research Association of Surgical Trialists (EUBREAST) found that compared to surgery or radiation therapy, chemotherapy to be associated with the highest risks for infection with SARS-CoV-2 and progression to COVID-19 in breast cancer patients. They assumed that radiation therapy would not have systemic effects on the patient and thereby no increased risks related to COVID-19. Hypofractionation of radiation treatments will reduce the number of hospital visits and thereby decreasing the risk [61]. Gowda *et al*. [62] provided guidelines for: general logistics and diagnostics, surgical, neoadjuvant and adjuvant treatment during the COVID-19 pandemic of cancer patients. Belkacemi *et al*. [17] suggested that in patients that are older than 65-70 years with lower risk stage I HR-positive/HER2- negative cancers and ductal carcinoma in situ (DCIS), radiation therapy can be replaced by adjuvant endocrine therapy. Juanjuan *et al*. [60] recommended that surgery can be delayed by months, while breast cancer patients are treated with neoadjuvant endocrine therapy.

The COVID-19 Pandemic Breast Cancer Consortium categorized breast cancer patients into three different levels of urgency of care across all specialties. Priority A: patients have conditions that are immediately life threatening or symptomatic requiring urgent treatment; priority B: patients have conditions that do not require immediate treatment but should start treatment before the pandemic is over; priority C: patients have conditions that can be safely deferred until the pandemic is over [63].

Prostate Cancer

Prostate cancer patients given certain treatments may have a survival advantage over others during the COVID-19 pandemic. These treatments include: novel hormonal agents including abiraterone, apalutamide, enzalutamide, hemotherapy-based docetaxel, Glucocorticoid receptor inhibitors and transmembrane protease, serine 2 inhibitors [2,64,65]. Prostate cancer patients receiving androgen-deprivation therapies appeared to be partially protected from the infection in early stage prostate cancer [66,67].

The start of radiation treatment and surgery for prostate cancer patients can be delayed in certain scenarios. Androgen deprivation therapy (ADT) can be used in more aggressive prostate cancer as a substitute for radiation therapy for several months, although a too long delay of radiation therapy may have a negative outcome. Extended neoadjuvant ADT can lead to extreme disease and death [68]. Stereotactic body radiotherapy can be considered as a safe treatment method for early prostate cancer [69]. Surgery should not be delayed more than two months in high risk and locally advanced patients. In low risk patients, surgery could be delayed in favor of active surveillance [17].

Chemotherapy on the other hand can increase the risk for viral infections and worsen the severity of the disease. Prostate cancer patients undergoing chemotherapy, including taxanes, have been shown to have an increased risk of viral infections, specifically influenza, which may worsen their morbidity and death as a result of immunosuppression caused by the chemotherapy itself [70].

Protocols for prostate cancer patients' handling during the COVID-19 period covering all aspects of the disease, such as diagnosis, staging, management based on stage and risk stratification, surgery, systemic treatment and radiotherapy were incorporated [67,71,72].

Comordities that lead to higher SARS-CoV-2 infection rates and death. Patients with metastatic castration-resistant prostate cancer (mCRPC) who received a second or more advanced treatment line, had a higher death rate in comparison to other comordities [73].

Kidney Cancer

In renal cell carcinoma (RCC) surgical resection should not be delayed for patients with locally advanced RCC such as cT3+ tumors, including all patients with renal vein and/or inferior vena cava thrombi as well as patients with high cancer progression or complications from the cancer. Planned partial or radical nephrectomy for lesser progressive tumors should be delayed, and interventional oncology ablative approaches should be considered in selected patients. Patients with several comorbidities should rather be treated with non-surgical therapies to reduce the risk of getting infected with COVID-19. Renal tumor ablation can be delayed for weeks or even months without affecting cancer related mortality [12,74].

Delaying in controlling RCC by means of therapeutic treatment can lead to an increase in risks of cancer development to metastasis and is associated with anxiety and stress. Patients with metastatic or recurring cancer, may be in need for hospital-based comforting care and symptom treatment. Chemotherapy or immunotherapy and recent surgery increases the risk for COVID-19 infection because of reduced immunity [15,74].

In kidney cancer many different mechanisms have been explored to combat COVID-19. Treatments of the cancer changed in some instances to oral agents including cabozantinib, sunitinib and pazopanib instead of nivolumab/ipilimumab to provide a survival advantage [2,75]. Curing of COVID-19 in kidney cancer patients include: monoclonal antibodies, oligonucleotides, repurposing current antivirals, convalescent plasma antibody transfer, blocking ACE2 receptors, ACE2 immunoadhesion strategy and endothelin receptor antagonists (ERAs) [15,76].

Kidney cancer patients with COVID-19 have a lower mortality than COVID-19 patients with other malignancies. The need for hospitalization is also lower that for thoracic tumor patients infected with COVID-19 [77].

Colorectal Cancer

Colorectal cancer makes out a large percentage of cancer patients that obtain COVID-19 and may have a higher mortality rate than other cancers [10,78]. This can be due to the neoplasm or to antineoplastic

therapies that lead to malnutrition and immunosuppression. Surgical treatment, the preferred treatment, also increases the risk of obtaining COVID-19, but delaying the surgery can lead to cancer severity progression as well as leading to an obstructive condition. Surgical treatment can be divided into three groups from where surgery can't be delayed, followed by where the time length of the delay can't be predicted for still being able to cure the cancer in some cases to a level where surgery can be delayed for a long period or alternative treatments can be used. Radiation therapy can be used to reduce the time spent in hospital [79].

Colon cancer metastasis is normally treated with poly-chemotherapy, extensive surgery and some targeted therapies that are responsible for a major decrease in immunity. On the other hand, thermal ablation induces low decrease in immunity if any, with then probably no risk of increasing the viral infection risk and severity. For oligometastatic patients with a small tumor burden and a possible curative intent, the treatment must not be delayed, and they must be treated with short hospital stay [12].

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. During the COVID-19 pandemic treatment for HCC can be divided into three stages: early-Stage HCC, intermediate-Stage HCC and advanced-Stage HCC. Interventional oncology should gain a leading role to cure or at least to control HCCs. Treatments of patients with HCC must proceed rather than delaying them due to the COVID-19 pandemic. There is greater risk for mortality among liver cancer patients due to delaying of treatments or delaying of liver transplants due to cancer patients living in high risk COVID-19 areas [12,80-82].

In patients with HCC and proven COVID-19, locoregional therapies should be postponed until recovery [12].

Conclusions

Italy, Spain and the USA suffered the most in the early stages of the world wide outbreak of COVID-19 and subsequently the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic on 12 March 2020. Cancer patients with comorbidities (hypertension, diabetes and cardiorenovascular diseases) can lead to severe illness and death as cancer patients have a higher risk of severe illness and death than COVID-19 patients without cancer. Severe COVID-19 reflects dysregulated inflammation and it has been repeatedly shown that inflammation could produce a hypercoagulable state in cancer patients. Cancer patients that obtain COVID-19 are treated according to the appropriate symptoms and oxygen therapy. Cancer patients that are prior cancer therapy, receiving therapy and post therapy are treated differently for the control of the progression of their cancers as well as the possibility of obtaining COVID-19. Cancer patients under active oncological therapy as well as who received anti-tumor therapy within 14 days before diagnosis are at elevated risk for severe complications and show a higher mortality rate due to COVID-19. A higher proportion of severe COVID-19 was also connected to immune checkpoint inhibitor treatments. It is reported that COVID-19 positive patients that had surgery are likely to be at higher risk of clinically severe events than those who did not have surgery. Postponing certain cancer surgeries may be associated with increased risk of progression; although the impact of surgical waiting times for different cancers may vary. For patients that already started with radiotherapy, finishing treatment is a priority, either following

initial planned fractionation schedules or after planned recalculation to shorten treatment duration. For patients who have not started radiotherapy yet, other treatment options must be investigated. Cancer patients receiving active chemotherapy treatment may be at greatest risk of both COVID-19 infection and severity due to increased immunosuppression. The clinical outcomes of patients with hematological malignancies were worse, with a mortality rate twice that of patients with solid tumors in a comparative study. Hematological malignancies, such as leukemia and lymphoma, can affect the immune system directly. The best treatment for solid cancers during the pandemic depends on the cancer type. Risks must be evaluated in connection with what therapy was the traditional, exclusive standard of care, what alternatives are there and whether combinations of different therapies will reduce the risk of obtaining COVID-19 and the severity of it. Multidisciplinary board meetings may be the way forward for the future for treatment of solid tumors.

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