Management of Cancer Patients during Coronavirus Disease 2019 Pandemic: A Literature Review

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ABSTRACT

Introduction: The number of confirmed cases of Coronavirus Disease 2019 (COVID-19) in the world has been increasing significantly since December 2019. Cancer patients are one of the vulnerable populations to become severe cases of COVID-19 or death when they are contacted with COVID-19. A treatment delay is associated with higher breast cancer-specific mortality and all-cause mortality. However, there is still limited data about how to manage cancer patients in this pandemic of COVID-19. This study aims to appraise the current evidence about the management of cancer patients during the COVID-19 pandemic.

Method: We searched and found 16 articles evaluating the management of cancer patients during the COVID-19 pandemic by searching in PubMed and EMBASE databases. We only included articles discussing COVID-19 and cancer in adults. There were three observational trials, four review articles, two case reports, six letters to the editor, and one guideline.

Results: There were several recommendations regarding patient care in the COVID-19 era. Firstly, outpatient visits, such as follow-up and surveillance of cancer patients, should be postponed. Alternatively, they can do teleconsultation, and their drugs will be delivered to their homes. Stratification and screening for the risk of COVID-19 infection should be done to those who needed urgent or emergency surgery. Otherwise, elective surgery should be postponed. However, several cases can be proceeded after discussion in the Multidisciplinary Team (MDT). Adjuvant and palliative chemotherapy should also be done as scheduled after discussing in MDT. Patients with ongoing radiation treatment should be continued as daily scheduled. Meanwhile, new patients should be carefully evaluated, and those with stable cancer can be postponed for treatment.

Conclusions: There is still scarce evidence related to the management of cancer patients during the COVID-19 pandemic. Further studies, in terms of stratification, risk, and management of cancer patients during the pandemic, need to be done to get better evidence on it.

INTRODUCTION

World Health Organization (WHO) declared COVID-19, caused by SARS-CoV-2, a public health emergency of international concern. Until now, the confirmed and death cases of COVID-19 have been increasing significantly in America, Europe, and, especially, Indonesia. As of April 7, 2020, the number of confirmed cases of COVID-19 had reached 1,279,722, with 72,614 deaths. In Indonesia, the number of cases reached 2,491 with 209 deaths [1–3].

Although susceptibility of cancer patients to severe COVID-19 has yet to be established, it is known that immunocompromised patients, such as cancer patients, are vulnerable to infections. Those, who are undergoing active treatment with chemotherapy or radiotherapy, are

thought to be at heightened risk of the severe stage from COVID-19, especially those with blood malignancy. Therefore, these patients might be at increased risk of COVID-19 and have poorer prognosis [4]. On the other hand, a delay to a single treatment modality is associated with higher breast cancer-specific mortality and all-cause mortality. Timely care throughout the continuum of breast cancer treatment is important for optimal outcomes [5].

The health-care institutions worldwide are taking precautions. Most cancer center hospitals have postponed non-urgent appointments and screened all people on entry [5,6]. There are different policies in the countries in Asia, Europe, and the USA. A retrospective clinical study of the initial COVID-19 cases indicated that 41.3% were due to hospital-related transmission [5]. Most hospitals had

canceled elective surgeries, but that was unlikely to affect most cancer patients [6]. There is limited data about the policy of cancer management during the COVID-19 outbreak. This study aims to appraise the current evidence about the management of cancer patients during the COVID-19 pandemic. The management focus on surgery, radiotherapy, and systemic therapy was reviewed followed by a practical recommendation. Additionally, supportive care and ethical issue in end-stage cancer were discussed.

Search Strategies

A comprehensive search of the literature was conducted in the PubMed (NIH) and EMBASE databases (January 2019 to March 2020) using keyword combinations of the medical subject headings (MeSH) of 'cancer care', 'cancer management', 'cancer treatment', 'COVID-19', 'coronavirus disease 2019', and 'SARS-CoV-2' on March 30, 2020. Management of adult cancer patients in the area of surgery, chemotherapy, and radiotherapy were the inclusion criteria. Firstly, we searched the titles and abstracts. Then, we evaluated the full text, whether they discussed cancer care in COVID-19 or not.

There were 16 articles focused on the management of cancer in the adult; those aged more than 18 years old were included. There were three observational trials, four reviewed articles, two case reports, six letters to the editor, and one guideline. The flowchart of the search strategy can be seen in **Figure 1**.

Figure 1. The flowchart of article search strategy

Risk COVID-19 to Cancer Patient

To the best of our knowledge, the study evaluated the risk of COVID-19 in patients with cancer was firstly reported

by college Liang et al. [4] published in The Lancet Oncology on Feb 14, 2020. The authors concluded that the proportion of patients with cancer histories was higher in a cohort with COVID-19 than in the non-COVID-19 population in China. Patients with cancer were more likely to develop COVID-19. They found 18 COVID-19 patients with cancer histories among 1590 COVID-19 patients from 575 hospitals in 31 provincial regions. The treatment status of 16 out of 18 patients was known. Four of 16 patients had undergone surgery or chemotherapy within the previous month, and the other 12 (75%) were cancer survivors with routine follow-up and had no immunosuppression therapy. They concluded COVID-19 infections in the 12 cancer survivors were associated with their cancer histories.

Patients with cancer had worse outcomes from COVID-19. In the study conducted by Wang et al. [7] it was reported that the median age of these patients was 63.1 years, which was significantly higher than the median age of those without cancer of 48.7 years. It suggested that older age might be associated with worse COVID-19 outcomes. Patients with cancer were observed to have a higher risk of severe events compared to those without cancer (7 [39%] of 18 patients vs 124 [8%] of 1572 patients $p = 0.0003$). Moreover, patients who underwent chemotherapy or surgery in the past month had numerically higher risk (3 [75%] of 4 patients) of severe clinical events than those who didn't (6 [43%] of 14 patients) after being adjusted with other risk factors including age, smoking history, and other comorbidities.

However, this observation is not enough to conclude that patients with cancer have a higher risk of COVID-19. The incidence of COVID-19 in patients with cancer would be more informative. There were only 18 patients, such a small number of patients with large amounts of heterogeneity, presenting as various cancer types with different biological behaviors and diverse treatment strategies. Those reported results might be due to a higher rate of smoking history in 18 patients with cancer [7]. Data has shown that tobacco use significantly increases the gene expression of angiotensin-converting enzyme, the binding receptor for severe acute respiratory syndrome coronavirus-2 [8]. The comparison between studies, reporting the risk of COVID-19 in cancer patients, can be seen in **Table 1**.

The other risk for patients with cancer is the difficulty of getting necessary medical services in terms of going to the hospital because of the outbreak. In Wuhan, the first epicenter of COVID-19 outbreak, more than 30,000 medical workers went there to help manage patients, prevent the spread, and contain the outbreak, so the other places had fewer doctors that would affect medical services outside the city of Wuhan [7]. There is still no data in Indonesia. Until this paper was written, Jakarta had been the epicenter of the outbreak in Indonesia. There were several major referral cancer centers there.

Table 1. The risk of COVID-19 in cancer patients

Authors (years)	Designs, sample size	Outcomes	Strengths	Limitations
Liang, 2020 [4]	Retrospective study, from China database, 1590 patients	Eighteen (1%) cancer history; 5 of 8 were lung cancer. Four (25%) of 16 patients had chemotherapy or surgery last month	Multicenter study, focus in cancer patients	Less detail about clinical and laboratory data
Wang, 2020 [7]	Retrospective, 138 hospitalized patients	Ten (7.2%) comorbidity of cancer patients infected. Four of 11 in ICU settings	First real data in hospitalized patients; complete evaluation of clinical laboratory day by day	Retrospective data, no control group in terms of risk factors
Chen, 2020 [13]	Retrospective single center, 99 cases	One (1%) cancer patient infected.	Complete evaluation of clinical laboratory day by day.	This was only from 1 center study, not intended to evaluate cancer patients

The Risk of Postponed the Schedule Cancer Treatment

Postponing cancer care will affect cancer survival because of the progressing of tumor. Yung et al. [5] found that a delay to a single treatment modality was associated with higher breast cancer-specific mortality and all-cause mortality. Timely care throughout the continuum of breast cancer treatment is important for optimal outcomes. Another study also found that the timing of surgery after neoadjuvant chemotherapy especially in ER+/HER-2+ patients more than 8 weeks resulted in decreased overall survival and disease-free survival [9]. We should discuss with patients and their families about balancing the risk between the progression of tumor versus the risk of getting contacted with COVID-19. The patients should be educated to observe the tumor size. If the tumor is progressing rapidly, they should contact their doctor for teleconsultation.

Problem in Diagnosis

COVID-19 infection can be mimicking the radiological features of a newly diagnosed cancer patient. In some cases, the comorbidity between lung nodules and COVID-19 can be challenging. In one case report, Qu et al. [10] described the atypical lung feature on chest Computerized Tomography (CT) of a lung adenocarcinoma cancer patient infected with COVID-19. In the early days of the disease, the typical ground glass from chest CT might not appear. There is only a typical lung mass nodule in the unilateral lung. The typical features from chest CT appeared in day 10 of the disease.

In hematologic malignancy patients infected with COVID-19, symptoms and laboratory findings might be atypical. Jin et al. [11] reported a male patient, with chronic lymphocytic leukemia and history of non-Hodgkin

lymphoma, came with 4 days of fever, sore throat, productive cough, and dyspnea. Laboratory findings showed increased white blood cells and increased lymphocyte percentage with moderate high-sensitivity C-reactive protein (Hs-CRP), and increased lactic dehydrogenase (LDH). The diagnosis of COVID-19 infection was confirmed from the CT scan of the chest showing bilateral ground-glass opacities. The increase in white blood cell and lymphocyte may shadow the typical laboratory findings in COVID-19.

Impact of COVID-19 Pandemic to Cancer Care

The actual impact of the COVID-19 pandemic has gone far beyond the viral infection itself and its related complications. It profoundly affects the entire health system and patients, including those who are not infected. Wang and Zhang pointed out that other aspects might be affected in cancer patients like the inability to receive the necessary medical services, especially surgery care. The potential risks postpone specialty outpatient visits, screening, oncology follow-up, and advanced diagnostics like endoscopy. Furthermore, hospitals of affected areas had to reallocate resources for pandemic while cancer patients were being sidelined because of the overwhelming number of COVID-19 patients in the intensive care units [4,7,12].

What Cancer Center Should Do

Health care facilities should be prepared for the early stages of the pandemic to receive suspected or confirmed patients with COVID-19 and patients while adjusting measures to protect cancer patients undergoing treatment, who have a higher risk of severe events or death than the general population. Healthcare workers need to be protected. Oncology waiting strategies,

prioritization of curative and adjuvant treatments over palliative were ones to limit the impact of COVID-19 to vulnerable patients. Oncologists should be prepared to manage patients with COVID-19 only in the case when the national health-care system is overwhelmed [14].

Surgery

In solid cancer patients, the main treatment option in the early stage is surgery. In patients with colorectal cancer, the 3-10-year survival would be lower if the treatment started more than 90 days since diagnosis. The ideal time, especially for colon cancer resection, is estimated to be between 3 to 6 weeks from the diagnosis, which is unlikely to be achieved during the COVID-19 pandemic. This will impact on the quality of care that may result in a deterioration of mild- and long-term results of cancer treatment. The increased waiting time to treatment was associated with the increased costs of care. Related to cancer care, alternative treatment to radical surgery in very early-stage cancer or very advanced disease, and centralization of patients were likely needed postoperative stays in intensive care units in few tertiary care hospitals [14,15].

All major elective surgeries for stable cancer should be postponed leaving intensive-care unit beds free during the peak of the pandemic. Surgical intervention needs to be prioritized although cancer surgery is not considered to be elective. There may be a two-week ban on elective surgery due to limited availability of Personal Protective Equipment (PPE), staff, and bed capacities. Elective surgery should be postponed or rescheduled after discussion in MDT if needed, and all patients need to screen for COVID-19 infection. In hormone-sensitive breast cancer, for instance, the treatment can be switched into several months of endocrine therapy and delay in surgery [16].

Radiotherapy

Radiotherapy in the specific condition is “life-saving” treatment and should be guaranteed to all cancer patients which is indicated. Failure to identify patients suspected or confirmed with COVID-19 would increase the risk of transmission to operators and other patients undergoing treatment. So, triage point at the entrance is the key to prevent all people from COVID-19 infection, including patients, caregivers, doctors, and supporting staff. A hydro-alcoholic solution for hand disinfection at the entrance of the radiotherapy center should be provided. PPE should be used for all health professionals and patients, according to the World Health Organization (WHO) indications. They should use sterile overalls (tunic and trousers), sterile disposable gown, FFP2 masks, clogs, and overshoes when treating patients with suspected of COVID-19 who need to continue radiotherapy according to medical indications [17].

For patients with stable cancer, radiotherapy treatment can be postponed up to 4-8 weeks. Patients with a progressive tumor should continue to receive treatment. When radiotherapy treatment is to be given, always use hypofractionation when possible. For palliative cases, such as cancer pain, use analgesics [16].

If a patient with pre-existing comorbidity has a cough, fever, or dyspnea symptoms, the patient should wear a protective mask, and radiotherapy should be continued. If a new cancer patient is tested positive for COVID-19, do not start the treatment. If a patient undergoing treatment is suspect, following the onset of COVID-19 typical symptoms and currently waiting for a microbiological diagnosis, they should stop the treatment. If a patient undergoing treatment is tested positive for COVID-19 and typically symptomatic, they should discontinue the current treatment. If a patient undergoing treatment is tested positive for COVID-19 but asymptomatic, they should discontinue the treatment [17].

Systemic Therapy

An intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer should be considered in endemic areas. Second, stronger PPE provisions should be made for patients with cancer and cancer survivors. Third, more intensive surveillance or treatment should be considered when patients with cancer are infected with COVID-19, especially in older patients or those with other comorbidities [12].

For solid tumor patients, selective adjuvant therapy with curative intent should proceed as scheduled despite the threat of COVID-19 infection during the treatment course. We should weigh the consequences of exposing our susceptible patients. We should reconsider switching to oral-systemic therapies. For patients with metastatic disease, treatment delays may lead to worsening performance status and loss of the treatment time window. A longer delay may lead to admission for symptom palliation [16]. Hence, we must rethink the effectiveness of further lines of palliative chemotherapy. Tailoring case by case and discussion in the MDT meeting by teleconference in cancer centers should be done regularly [18].

Patients with aggressive blood malignancy have similar urgency for life-saving treatment. Stem cell transplantation and cellular immunotherapies provide curative treatments in such aggressive disease and cannot be delayed. Cryopreservation of donor products has been recommended due to travel restriction that limits access to international donors for allogeneic stem cell transplantation. The treatment can be adjusted by lessening the immunosuppression, moving the patient from the inpatient to outpatient clinic, and delaying the treatment [19].

There is still limited data on whether cancer treatment using targeted therapy should be discontinued.

Cancer patients with concomitant COVID-19, who use targeted therapy, Osimertinib, can safely use it until they are discharged. However, further studies are needed to confirm this outcome [20].

Recommendation From Recent Published Data

Until this paper was submitted, there are still limited recommendation of cancer management during COVID-19 pandemic. For patients with cancer who do not need intensive therapies, homecare options should be considered, such as telemedicine and mobile health-care devices. Remote monitoring could be a good option for follow-up for ambulatory patients with COVID-19. Further recommendation can be seen in **Table 2**.

Other Treatments

Generally, anti-COVID-19 therapy should be prior to or combined with other therapies, including anticancer treatment. Acupuncture and massage involve close contact with cancer therapy and are widely used to relieve and control a variety of symptoms in cancer patients. However, this treatment is unlikely to be done in the endemic area because of the physical distancing rule. Other supportive treatments, such as Tai Chi and Qi Gong, may be suitable for indoor exercises [21].

Another integrative therapy, Chinese Herbal Medicine (CHM), was widely used in the treatment of COVID-19 and was described to be quite effective in preliminary clinical practice. China's national protocol has included CHM therapy in the management of cancer patients diagnosed with mild or moderate cases of COVID-19, and it was given to the patients, especially the elderly

and those with complications. Further studies should evaluate the CHM role in COVID-19, especially on cancer patients [21,22].

Ethical Consideration

In the pandemic situation, oncology patients confirmed positive for COVID-19 with the late-stage disease or comorbid health conditions, such as heart or lung dysfunction, require mechanical ventilation that has a poorer prognosis. According to a recent retrospective study from Wuhan, China, only one patient survived among 32 COVID-19 patients who were seriously ill and required mechanical ventilation [23]. The decision should be discussed between the oncologist and palliative care team about the end-of-life care on cancer patients who become infected with COVID-19. Oncologists should also consider the treatment most likely to be successful, symptom-relieving, or lifesaving, and interventions with the greatest benefit [16].

CONCLUSION

There is still scarce evidence related to the management of cancer patients during the COVID-19 pandemic. In this difficult time, new cancer patients infected with COVID-19 will be reported. We will learn from the observed cases. International registry is needed to gather information regarding management cancer patients with COVID-19. Further studies, in terms of stratification, risk, and management of cancer patients during the pandemic, need to be done to get better evidence on it.

Table 2. Recommendation for management of cancer patients during COVID-19 outbreak [15-17,19]

Management	Reduce number of staffing at minimum level. Cancel all unnecessary activities (meetings, trainings, clerkship student rotations). Make alternative teams with competency COVID-19. Triage all patients (temperature check, screening before entering emergency unit, use PPE according to risk areas).
Outpatient visits	Postpone outpatient visits: cancer follow-up and surveillance. Phone or teleconsultation for ambulatory cancer patients and drugs delivery to home.
Routine procedures	Postpone and reschedule elective surgery after discussion in MDT, if needed the patients need to screen for COVID-19 infection. Adjuvant and palliative chemotherapy should be done as scheduled after discussing case by case in MDT meeting. Chemotherapy as scheduled in urgent case of hematologic malignancy. Patients with ongoing radiation treatment should be continued as daily scheduled, whilst new patients should be carefully evaluated and patients with stable cancer can be postponed for treatment.
Urgent procedures	Stratify the risk and screen patients for COVID-19 infection (rapid test) who need urgent or emergency surgery. Standard PPE for low-risk and intermediate-risk patients (Lower GI endoscopy). Advanced PPE for high-risk patients and intermediate-risk patients (Upper GI endoscopy). Performed endoscopy if needed in a negative pressure room.

PPE, Personal Protective Equipment; COVID-19, Coronavirus Disease 2019; GI, Gastrointestinal; MDT, Multidisciplinary Tumor

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