

A Systematic Scoping Review of Cancer Patients' Treatment during the COVID-19 Pandemic

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Abstract

Amongst the global effects of coronavirus disease (COVID-19), one of the challenges faced by health practitioners is how to continue offering treatment to cancer patients. This crisis has led to the collaboration of medical experts to discuss new strategies in the wake of this pandemic. Oncology treatment guidelines have been modified around the world to ensure the safety of this immunocompromised population by reducing exposure to coronavirus through different isolation and teleconsultation measures while providing life-saving treatments in these unprecedented settings. This scoping review summarizes the changes in the treatment of cancer patients as mentioned in the most up-to-date literature available through the first half of the year 2020. It is composed of narrative reviews, discussion or opinion papers, and reviews of current treatment guidelines for multiple types of cancers, including the extra measures needed to avoid infection. This paper aims to provide evidence-based decisions on how to deliver treatment effectively without compromising cancer patients' safety.

Keywords: COVID-19; SARS-CoV-2; Cancer Treatment; Pandemic

Introduction

The emergence of a novel respiratory disease, COVID-19, or acute respiratory syndrome coronavirus (SARS-Cov2) caught the whole world by surprise. This infection was initially reported in Wuhan, China in December 2019 and rapidly spread around the world. In March 2020, it was declared a pandemic by the World Health Organization [1]. According to the WHO website, as of August 12, 2020, 216 countries, areas and territories were affected, with a total of 20,405,695 confirmed cases and with 743,487 deaths globally [2]. This infection was reported as a zoonotic disease and characterized by rapid human-to-human transmission through contaminated droplets. Initially estimated mortality rates were at 11% - 15%, but recent data shows 2% - 5% [3].

The presenting signs and symptoms in COVID-19 infection can vary from asymptomatic to acute life-threatening respiratory distress. Cancer patients are already vulnerable because of their immunocompromised status, either due to cancer itself or from the cytotoxic therapies. They are at a higher risk of contracting the infection [4,5]. A multi-center retrospective cohort study evaluated the association

of clinical manifestation and risk factors with the COVID-19 disease severity and it showed that cancer patients are 3.6 times more likely to develop severe COVID-19 infection compared to the general population [6]. COVID-19 infection greatly affected several large-scale activities, including the delivery of health care services to people with chronic conditions such as cancer [7]. Any disruption in the provision of the standard of care for the cancer population will likely result in an unfavorable consequence [8]. A study done in China showed that a cancer patient in active treatment (surgery and chemotherapy) is predicted to have a dismal outcome resulting in intensive care admissions or death [7]. Normally, cancer patients go to the hospital for their treatment and follow up, which puts them at high risk for contracting COVID-19. Despite strict quarantine protocol and symptoms surveillance, nosocomial acquired transmission of the virus was still reported [9], thus highlighting the importance of effective infection control. The challenges now lie with oncology professionals on how to navigate this difficult balance of providing the standard of care, and at the same time keeping patients away from health care facilities as a preventive measure against infection.

Purpose of the Study

The purpose of this scoping review is to identify modifications to or recommendation for guidelines for cancer treatment that intend to mitigate the spread of the COVID-19 infection.

Materials and Methods

Research questions

The six authors included the following questions to guide this systematic scoping review of cancer patients' treatment during the COVID-19 pandemic:

1. Is there any modification or recommendation to the treatment guidelines for cancer patients due to COVID-19?
2. Is there an alternative management choice to the gold-standard treatment for cancer patients due to COVID-19?
3. Are there any scheduling changes in the delivery of oncological treatment due to COVID-19?
4. Are there any extra precautions for inpatient/outpatient visits for cancer patients during their treatment due to COVID-19?

Selection of relevant studies

For the systematic search, the authors used PubMed, Cochrane Library, and Google Scholar. The detailed search strategy, conducted on July 8th, 2020, used "cancer treatment*" AND "COVID-19*", and was limited to articles written or translated into English. The published date was kept open but there is no registry of COVID-19 related articles before December 2019, and the articles included in the review ranged from January to July 2020.

Study selection criteria

Six authors screened citation titles and abstracts, then reviewed full articles (n = 76) and considered articles that were relevant to the research questions and discussed cancer patients' treatment during COVID-19 (n = 29). Articles were excluded if they were abstract only or focused on clinical trials.

Data extracting process

An Excel file for data-extraction was created by the six authors, and it was used to code the study variables. Data were extracted and continuously updated in the file. The following data items were extracted: general information (author's name, article title, country of origin, publication date); methodological data (the type of article, type of cancer); and content of the articles that corresponded to the research questions of this review. No formal critical appraisal of primary studies for this scoping review was performed.

Presenting results

Results are presented under the following categories:

- Modification or recommendation to the treatment guidelines for cancer patients due to COVID-19.
- Alternative management choice to the gold-standard treatment for cancer patients due to COVID-19.
- Scheduling changes in the delivery of oncological treatment due to COVID-19.
- Extra precautions for inpatient/outpatient visits for cancer patients during their treatment due to COVID-19.

The literature search identified 76 articles and reports, of which 29 were eligible for inclusion in this scoping review (related to cancer patients' treatments during the COVID-19 pandemic). The review has been reported following the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines as illustrated in figure 1.

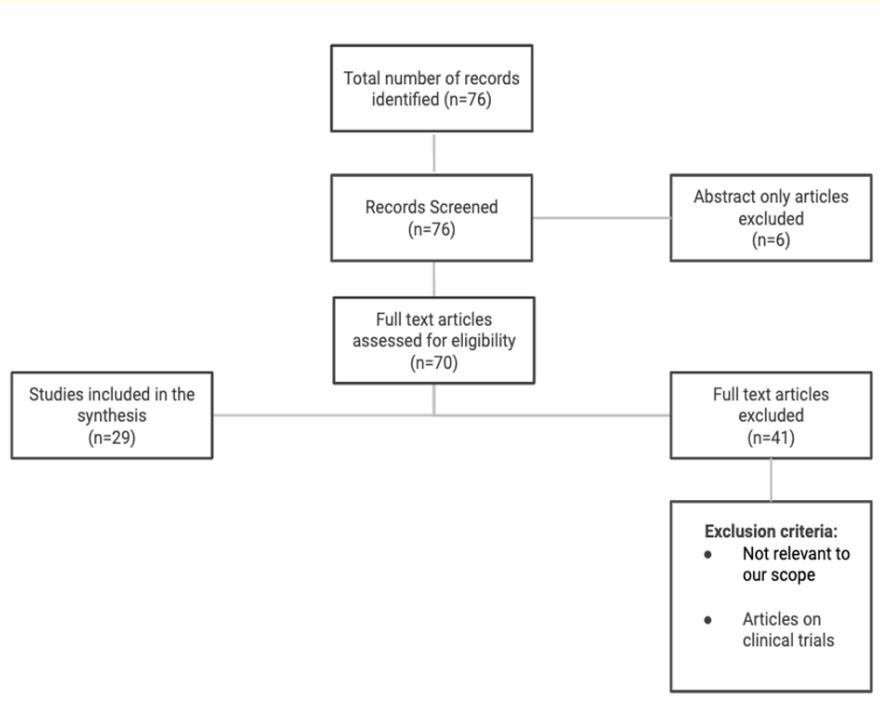


Figure 1: Study flow chart.

Results

This scoping review includes 29 articles from five reviews of guidelines from USA, China, India, UK, Italy Europe, and other countries discussing general cancer, lung, ovarian, endometrial, cervical, gestational, trophoblastic neoplasia, colorectal and rectal cancer; one systematic literature review/meta-analysis from the USA about endometrial, vaginal, breast and prostate cancer; six discussion paper/opinion paper/editorial/protocol from Nigeria and USA about general and urogenital cancer; fifteen narrative review/rapid review from the USA, Multinational, Brazil, Italy, Saudi Arabia, and Germany on breast, lung, rectal, general, head and neck, mixed (hematology and solid tumors), hepatocellular, sino nasal and anterior skull base; and two surveys/qualitative study from Netherlands/Italy about general (various types) cancer. The study characteristics of the included articles are shown in table 1.

Type of Articles	Number of Articles	Authors	Cancer Type
Review of Guidelines	5	Marijnen., <i>et al.</i> 2020 Europe; Saverio., <i>et al.</i> 2020, Italy; Ueda., <i>et al.</i> 2020, USA; Uwins., <i>et al.</i> 2020, Multinational; Zhao., <i>et al.</i> 2020, China	Rectal Cancer, Colorectal Cancer, General, Ovarian, Endometrial, Cervical, Gestational Trophoblastic Neoplasia, Lung cancer
Systematic Literature Review/ Meta-analysis	1	Williams., <i>et al.</i> 2020, USA	Endometrial, Vaginal, Breast, and Prostate cancers
Discussion Paper/ Opinion Paper/ Editorial/ Protocol	6	Marti., <i>et al.</i> 2020, Spain; Mirnezami., <i>et al.</i> 2020, UK; Mistrella., <i>et al.</i> 2020, Italy; Nguyen., <i>et al.</i> 2020, USA; Salako., <i>et al.</i> 2020, Nigeria; Vidya., <i>et al.</i> 2020, Multinational	Breast (2), Rectal, Urogenital, General (2)
Narrative Review (Review)/ Rapid Review	15	Alshamrani., <i>et al.</i> 2020, Saudi Arabia; Baldotto., <i>et al.</i> 2020, Brazil; Barry., <i>et al.</i> 2020 Multinational; Dingemans., <i>et al.</i> 2020, Multinational; Han., <i>et al.</i> 2020, USA; Maio., <i>et al.</i> 2020, Multinational; Omarini., <i>et al.</i> 2020 Italy; Patel., <i>et al.</i> 2020, USA; Singh., <i>et al.</i> 2020, USA; Sheng., <i>et al.</i> 2020, USA; Skowron., <i>et al.</i> 2020, USA; Specht., <i>et al.</i> 2020 USA; Sternberg., <i>et al.</i> 2020 Brazil; Turri-Zanoni., <i>et al.</i> 2020 Italy; Vordermark, 2020, Germany	General (5), Lung (3), Hepatocellular, Head and Neck (2), Mixed (Hematology and Solid Tumors), Breast (2), Rectal, Sinonasal and Anterior Skull Base
Survey/Qualitative Study	2	Indini., <i>et al.</i> 2020, Italy; de Joode., <i>et al.</i> 2020 Netherlands	General (2)

Table 1: Study characteristics.

The following sections describe the summary of the key findings in the available literature of treatment for cancer patients organized by research questions.

Modification or recommendation of the treatment guidelines for cancer patients due to COVID-19

Recommendations or modifications to guidelines consider the addition of COVID-19 screening and testing before any provision of treatment (Table 2). This recommendation was stated across numerous different studies to continue oncological management for aggressive cancer types and late stages with a possible delay of elective benign surgeries. It was also suggested to prefer adjuvant therapy (AT)

for responsive cancers or early-stage, as well as considering treatment schemes that reduce virus transmission spread, such as minimally invasive surgeries, avoiding procedures that involve airway manipulation with special care during intubation/extubation procedures, and the use of alternative peripheral anesthesia methods over general anesthesia. Besides, certain treatment modalities have an increased demand during the COVID-19 pandemic such as radiotherapy (RT) with hypo-fractionated schedules and immunotherapy with dosage changes as an adjuvant approach to decrease the frequency of hospital or clinic visits. Table 2 summarizes all the modifications and recommendations made to cancer treatment guidelines across the studies in our scoping review.

Modification or recommendation of the treatment guidelines for cancer patients due to COVID-19
<ul style="list-style-type: none"> • Recommendations on transferring patients to Phase 1 hospitals with few COVID-19 patients. Several institutions also recommended a personal air-purifying device for patients with unknown COVID-19 status [10,11]. • For all cancer types, 'elective benign surgery' should cease and oncological treatment should continue based on prioritization according to cancer stage and severity and to avoid delays in the management of aggressive cancer types with a direct referral of newly diagnosed cancers to a multi-disciplinary team [12-17] • During the COVID-19 pandemic, there is an increased demand for radiotherapy, such as stereotactic body radiation therapy for lung cancer, with a preference for lower-fractionated schedules. External beam therapy or radiotherapy should be preferred over brachytherapy for lung cancer where possible. Brachytherapy should be prioritized for cervical cancer [10,13,17-19]. • For hematological cancers, cryopreservation of donors is recommended to optimize the availability of treatment since travel bans would decrease donor availability. Patients with immunosuppression treatment should be assessed individually to decide transfer to outpatient management or delay [16]. • Minimally invasive surgeries and techniques such as VATS (Video-assisted Thoracoscopic Surgery) with protective measures are recommended in articles for colorectal, gynecological, and lung cancers. Where possible, a move toward same-day discharge can be made for many oncology procedures [10,17,20]. • Strong consideration to have only anesthesia staff in the room during intubation/extubation and implementing a waiting period before staff re-entry into the room after extubation. Also, to increase awareness of the ventilator filter system. For lung cancer, avoid procedures with airway manipulation (i.e. EBUS, Bronchoscopy, spirometry) and pursue image-guided transthoracic biopsies over transbronchial approach for diagnosis [10,18,21]. • Patients prone to lung infections or presenting with respiratory symptoms and surgical candidates at the highest risk of contagion spread should complete history screening, and SARS-CoV-2 tests to rule out COVID-19. As testing capabilities expand, testing before chemotherapy delivery may be considered. Perform chest CT scan 24 - 48 hours before surgery, to assess the presence of suspected lesions for COVID-19 [10,18,21-23]. • In gynecological cancer procedures and any other surgeries, avoidance of general anesthesia is recommended in scenarios where alternate anesthesia methods are possible. For gynecological cancer local disease control, curative radiotherapy should be prioritized over adjuvant therapy [17,24]. • Immune checkpoint inhibitors therapy is a suitable option during the COVID-19 pandemic either alone or in combination with chemotherapy. Consider delay methods, such as oral Etoposide for SCLC lung cancer and oral progesterone for endometrial cancer, in early stages to reduce the frequency of hospital visits. Restrict certain procedures to highest-risk patients i.e. vaginal cuff boost for cervical cancer [10,13,17,24-26].

Table 2: Modification or recommendation of the treatment guidelines for cancer patients due to COVID-19.

Alternative management choice to the gold-standard treatment for cancer patients due to COVID-19

Several identified articles suggested postponing surgical intervention during the COVID-19 pandemic (Table 3). Some articles suggested performing simple oncological procedures for low-grade breast tumors and ductal cancer *in-situ* (DCIS) [27]; increasing RT or chemotherapy in head-and-neck, lung, cervix, esophageal, and prostate cancer [19,28]; preferring radical RT with concurrent chemotherapy (CT) for vulvar cancers [17]; as well as neoadjuvant therapy for lung cancer [13,15]; advanced ovarian cancer [17] and endocrine therapy for breast cancer [24,27,29] to mitigate effects caused by surgery postponement. Likewise, an article recommended continuing neoadjuvant chemotherapy before surgery for the patients of human epidermal growth factor receptor 2-positive breast cancer [23]. However, elderly or co-morbid patients were taken in consideration of radiotherapy or chemotherapy omission [17,19]. Nevertheless, AT is a common practice in cancer patients' treatment in normal times, and we found considerations about stopping or delaying them in treatment for lung cancer [18] and ER-positive early-stage breast cancer [28] depending on the stage of cancer and patient's outcome. For those patients who have already started AT, it is advised to reduce the duration in Stage III colon cancer, early ovarian, or breast cancer [28]. Reducing the number of doses while increasing the amount in HDR BT (high dose rate brachytherapy) was advised in uterine cancer [24].

During the pandemic, some treatments of choice were modified and priority was given to targeted therapy over CT/immunotherapy in lung cancer [10]. Oral drugs were preferred to continue treatment at home after surgery for lung cancer patients in earlier stages [21]. Oral targeted drugs were chosen for metastatic lung cancer patients with an extra observance on the patients' outcomes [21]. In one study, breast BT was preferred after breast conserving surgery [24]. For high-risk prostate cancer, androgen deprivation therapy was recommended in several contexts [24]. In an observational study for locally advanced rectal cancer, delayed surgery was considered after a short course of CT [30]. Improved outcomes and effectiveness were observed while taking this into consideration. Oral CT was suggested instead of systemic therapy.

Changes in the schedule of oncological treatment delivery due to COVID-19

Modifications to the schedule for delivery of different treatments were considered (Table 3). Gynecological cancers will be assessed according to the individual cancer stage burden, differences in outcomes, and survival rates [16]. Delaying treatment could span between 4 - 8 weeks and doses of interventions could be modified to the safest possible level to reduce the number of visits and exposure [17,24]. For lung cancers in early-stage, surgery delays are possible whenever tumors are responsive to AT (10,21). For colorectal cancer, further cycles of CT are recommended, if surgery is not possible or unsafe in the setting of COVID-19 [31,32]. One study recommended the use of vincristine/dexamethasone pulses every 12 weeks rather than every 4 weeks on pediatric patients with standard-risk B-Cell acute lymphoblastic leukemia [33]. Overall, articles recommended delaying necessary surgeries according to individual cases for at least 2 weeks but no more than 2 months in patients with COVID-19 symptoms or confirmed infection [20,21]. There is also one instruction manual for same-day breast reconstruction surgery to conserve resources and minimize postoperative risk [34].

Extra precautions for inpatient/outpatient visits for cancer patients during their treatment due to COVID-19

Multiple additional precautions were found across the studies (Table 4). Isolating measures were taken during COVID-19, such as social distancing in outpatient waiting areas [17,35], implementation of solutions to conserve personal protective equipment (PPE), reduced number of individuals present in rooms, and restricted number of visitors to 'none' or 'single-only' [10,16,17,22,35]. It was also considered the establishment of triage stations outside the hospitals, single-points of entry, as well as a multilayer coverage system for the clinics in case providers had to be quarantined on short notice [16,22,35,36], moreover, awareness among health professionals was raised regarding these new infection control measures. In addition, other interventions were harnessed such as pooling of resources which include shifting patients to COVID-free units/hospitals [17,35], and assignment of dedicated wards and operating rooms for COVID-19 and non-COVID-19 patients with cancer [16,17,26].

<p>Alternative management of choice to the Gold-Standard treatment for Cancer Patients due to COVID-19</p>	<p>Summary of findings Limited surgical care with perioperative COVID-19 testing for head and neck cancer Simple oncoplastic procedures for low-grade breast tumors and ductal cancer <i>in situ</i> (DCIS) Increasing radiotherapy or chemo-radiation was suggested in head-and-neck cancer, lung cancer, cervix cancer, esophageal cancer, and prostate cancer Consideration of stopping or delaying adjuvant therapies in treatment for lung cancer and ER-positive early-stage breast cancer Reduce therapy duration in stage III colon cancer, early ovarian or breast cancer Reducing the number of doses while increasing the dose in HDR BT was advised in uterine cancer Oral drugs, brachytherapy, and androgen deprivation therapy were preferred in several cancer patients' treatments Delayed surgery was considered after short-course chemotherapy for locally advanced rectal cancer Oral chemotherapy instead of systemic therapy was suggested</p>
<p>Changes in the schedule of oncological treatment delivery due to COVID-19</p>	<p>Summary of findings Gynecological cancer studies would allow up to 8 weeks delay Early-stage lung cancer surgery can be delayed if a response to adjuvant chemotherapy is possible Further cycles of chemotherapy considered on colorectal cancer Pediatric patients with B-Cell ALL can have modified-shortened V/D* pulses as per NCI** Same day breast reconstruction to avoid post-op delays</p>

Table 3: Alternative management of choice to the gold-standard treatment and changes in the schedule of oncological treatment delivery.

*V/D: Vincristine/Dexamethasone; **: National Cancer Institute (USA).

<p align="center">Extra precautions for inpatient/outpatient visits for cancer patients during COVID 19</p>
<ul style="list-style-type: none"> • Multilayer coverage system for the clinics, social distancing, triage stations outside the hospital, and restrictions on visitors • One point of entry, personal protective equipment (PPE) • Improving awareness of preventing COVID-19 infection among medical professionals • The pooling of resources, separate wards, and operating rooms for COVID-19 patients • Endoscopy in negative pressure room • Collaboration between pharmacy departments • Home administration of chemotherapy, subcutaneous medications, and supportive care therapy • Sending medications by postal carriers to patients' homes • Pharmacies dispense more medication supply for longer durations • Digital health platforms to limit patients and oncology professional's physical interaction • Provide telemedicine services to cancer patients and their caregivers • Screening for COVID symptoms by virtual communication a day before appointments • For cancer patients in remission or non-progressive stage, conduct consultation via telemedicine • Increase telephone/virtual communications between surgeon and patient before the decision to delay surgeries

Table 4: Extra precautions for inpatient/outpatient visits for cancer patients during COVID 19 from literatures.

To limit patient visits to hospitals and clinics during the COVID-19 pandemic, providers should strongly consider administering CT [26] and subcutaneous medications [10] at home when feasible. Pharmacies can dispense more medication supply for a longer duration, sending medications by postal carriers to patients' homes and the use of drive-through medication collection areas--for example, 2 - 3 months' supply instead of the monthly quantity [33]. Virtual clinics should be initiated for the management of stable patients [33,37] and during post-operative monitoring and cancer surveillance [14]. Three types of telemedicine are suggested, each with its specific use: a) Tele-guidance, to carry out guidance and referral of patients in isolation; b) Tele-monitoring, to monitor patients remotely; and c) Tele-interconsulting, exclusive for multidisciplinary professional consultation, exchange of information and opinions, and diagnostic or therapeutic assistance [15,28,35,36]. In-person consultation should be reserved only for emergency and urgent concerns [36].

Discussion

There were 76 articles primarily identified from which 29 were given insights on the treatments for cancer patients considering the COVID-19 pandemic. There were 35% of the articles (n = 10) focused on cancers in general, 17% of the articles were on breast cancer (n = 5) and 14% on lung cancer (n = 4). Three articles were found on rectal cancer, two for endometrial, and two for head and neck cancer. Articles on each subtype were found for vaginal, prostate, ovarian, cervical, colorectal, urogenital, hepato-cellular, sino-nasal and anterior skull base cancers.

Oncological patients have a higher mortality risk due to COVID-19 [38]. Most articles focused on modifications or recommendations to treatment guidelines for cancer patients in this unprecedented situation. Commonalities were observed in the approach of the treatment for cancer patients. All the recommendations mentioned in the articles are summarized to get several treatment approaches at a glance. Many articles proposed some alternative management of choice to the gold-standard treatment. Depending on the context, changes were done in adjuvant therapy (AT), chemotherapy (CT), and radiotherapy (RT), among others. All these changes were either suggested or implemented to mitigate the spreading of SARS-CoV-2 infection.

It was found that these modifications have produced changes, such as suspensions or delays, in the schedule of oncological treatment. A multi-center study also revealed that COVID-19 has increased the vulnerability of cancer patients [39]. These concerns were addressed in some studies and different approaches were taken to mitigate the risks such as taking extra precautions in the approach to the different treatments. Considering the high risk of severe outcomes in these patients due to COVID-19 [40], several studies suggested practicing strict protective measures specifically while treating cancer patients. For example, isolation measures, triage, visitor restrictions, dedicated wards and operating rooms, and telemedicine modalities [15,28,35].

There are some limitations in this scoping review. The search result is dated July 8th, 2020. Numerous articles were published after this date, which may also be relevant but are not included in the study. Quality assessment of the studies was not addressed in this scoping review. A systematic search was performed in three databases Cochrane Library, Google Scholar and PubMed only.

Conclusion

As per the review of currently available studies, it is an undeniable fact that cancer patients are at higher risk due to COVID-19, and treatment for these patients is a crucial factor. The efforts are ongoing to minimize any decrease in quality of care in the wake of this pandemic. The medical fraternity worldwide contributed special precautions to prevent viral spread and new treatment guidelines. Following these recommended, necessary, and timely steps in treatment interventions while taking appropriate protective measures can save cancer patients from severe outcomes or death due to COVID-19.

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