Key Research Question:

What is the optimal strategy for assessing patients who were infected with COVID-19 for suitability for starting or resuming cancer treatment?

a. What criteria can be used to assess both clinical suitability for proceeding with therapy in the setting of recent infection, as well as infection control criteria to reduce risk of transmission of COVID-19 in cancer care environments?

b. What criteria should be used to ensure that patients are well enough to have cancer treatment after COVID-19 infection?

Context

- Delivering cancer treatment during the COVID-19 pandemic is challenging given that cancer patients are at increased risk for serious complications from COVID-19.
- Cancer patients may have extra considerations for both recovery from infection and risk of transmission of infection due to immunocompromise from their underlying condition and its therapies.
- To lower the chances of COVID-19 infection among cancer patients and staff, all patients and visitors in Alberta are screened before their appointments at the cancer centre (questionnaire and temperature check) [1]. Decisions for clearing cancer patients infected by COVID-19 so they can safely initiate (or re-initiate) cancer treatment are currently made by cancer teams, based on their expertise and opinion.
- This rapid review has been based upon limited literature related to COVID-19 and cancer, existing published guideline documents related to the COVID-19 pandemic, and clinical experience with the SARS and MERS coronaviruses, as well as experience in influenza epidemics.
- This review does not address the following aspects related to standard strategies for clearing patients for cancer treatment: 1) increased risk of suffering toxicities related to treatment, 2) consent from patients to proceed with treatment.
- The information in this rapid review is meant to be used in addition to clinical judgment and knowledge of the patient.

Key Messages from the Evidence Summary

- Cancer patients may be more susceptible to infections than individuals without cancer by virtue of their cancer therapy and sometimes their underlying disease, and at increased risk for serious complications related to a COVID-19 infection.
- Cancer patients with COVID-19 who have undergone or are undergoing cancer treatment (specifically within a month of infection) might be at increased risk of worse outcomes from a COVID-19 infection.
- There is no evidence available to guide assessing recovery from COVID-19 for cancer patients. The recommendations presented in this review are made primarily based on the increased risk of poor outcomes in patients with cancer who have been infected with COVID-19.
- For cancer patients with COVID-19 it is recommended that cancer treatment is deferred until symptoms of COVID-19 have resolved and the virus is no longer detectable by RT-PCR, unless the cancer is rapidly progressing and the risk-benefit assessment favours proceeding with cancer treatment. There is a lack of data overall on the correlation between RT-PCR positivity and the presence of replicating or infectious
virus in immunocompetent and immunocompromised hosts. Given that, there are a variety of symptom based and/or swab based strategies in determining infection control strategies in different settings, for example, assessment of HCW return to work may be based on time elapsed since symptom onset rather than swab results.

- As a precaution pending further data, test-based strategies for discharging COVID-19 patients have been recommended to guide therapy decisions as well as infection control considerations. AHS guidelines recommend that after symptom resolution, at least 2 negative approved RT-PCR specimens collected at least 1 week apart from all previously positive sites are needed before discontinuing precaution.
- There are no accepted guidelines to ensure safe initiation (or re-initiation) of cancer treatment after a COVID-19 infection. Expert consensus suggests reasonable durations of delay are >3 months for cancers with low risk progression, 3 months for cancers with intermediate risk of progression, and no delay for cancer with high risk of progression depending on the patient context and prognosis.

Committee Discussion

The committee achieved consensus on the key messages and recommendations. The committee reviewed the recommendations and felt that the overall clinical parameters would be the single most appropriate factor in decisions around cancer therapeutics post COVID, particularly in settings where therapy is required urgently. In less urgent situations, deferring at least until the patient is recovered and meets the AHS guidelines for isolation precautions (which would generally be a duration of 2-4 weeks) is reasonable, with guidance for acceptable durations based on the likelihood of progression of the underlying disease. It was acknowledged that further evidence around the correlation of positive RT-PCR with infectious and replicating virus in COVID-19 may alter these recommendations.

Recommendations

1. For cancer patients infected with COVID-19 it is generally recommended that the initiation (or re-initiation) of non-urgent cancer treatment is deferred until symptoms of COVID-19 have resolved, the patient is at least 14 days from the onset of COVID symptoms, and the virus is no longer present, as evidenced by 2 negative nasopharyngeal swab tests performed 7 days apart. Even then, such patients requiring non-urgent cancer treatment could potentially benefit from further treatment delays during a pandemic when healthcare resources may be limited to both deliver therapy and support patients who develop complications from therapy (see Recommendation 2). For other cancer patients in need of urgent cancer treatment, it is recommended that initiation (or re-initiation) of treatment is deferred at least until symptoms of COVID-19 have resolved, and the virus is not detected on 1 nasopharyngeal swab test. To ensure safety of other patients and healthcare workers, Alberta Health Services’ Infection Prevention and Control isolation recommendations for immunocompromised patients should be respected when such patients receive urgent cancer treatment. Droplet and contact precautions are required until these patients are free of COVID symptoms, are at least 14 days from the onset of symptoms, and have had 2 consecutive negative COVID-19 RT-PCR swab tests performed at least 7 days apart.

2. Reasonable time ranges of deferral of cancer therapeutics to allow convalescence and optimal healthcare supports are suggested as follows: >3 months may be acceptable for cancers with low risk progression, and 1-3 months for cancers with intermediate risk of progression. There are no deferrals for cancer therapeutics recommended in patients with high risk of progression.

3. Patients should fulfill standard eligibility criteria for the specific cancer treatment (e.g., adequate performance status and organ function), and provide informed consent considering relative risks and benefits of the specific treatment [2].
Summary of Evidence
Credible information sources were identified through a rapid online search performed by Knowledge Resources Services, within Alberta Health Services, and writers of this review. Six references are original research (including four articles related to COVID-19 [3-7], and one related to prior viral respiratory outbreaks [8]), three are article reviews [9-11], and six are commentaries [12,13], opinion papers [14] or research letters [15-17]. Two of these references have not been peer-reviewed [3,7]. In addition, 17 references are publications produced by expert panels [18-21] or by local, national and international health organizations and/or authorities in response to managing the COVID-19 or similar pandemics [1,2,22-32] which use a range of research sources and likely expertise consensus within these organizations. Eight of these references are Alberta internal policy documents [1,2,25-28,30,31]. Key limitations of this review:

- Rapid turnaround time resulted in a limited time to conduct a thorough search of the research and grey literatures.
- Given the rapidly changing information and literature related to COVID-19, the literature available is limited primarily to guideline documents, published letters, and descriptive papers.

Evidence from existing policies and guidelines
Governments across the globe have made it clear that cancer treatment should continue to be prioritized whenever possible during the COVID-19 pandemic. For cancer patients with a confirmed COVID-19 infection it is established that, unless the cancer is rapidly progressing and the risk-benefit assessment favours proceeding with cancer treatment [19], patients should be assessed for holding cancer treatment until symptoms of COVID-19 have resolved and there is some certainty that the virus is no longer present.

a) **What criteria can be used to assess both clinical suitability for proceeding with therapy in the setting of recent infection, as well as infection control criteria to reduce risk of transmission of COVID-19 in cancer care environments?**

There is a paucity of research on follow-up of recovered COVID-19 patients [15]. There is no evidence to speak to the question of whether or not cancer patients who have been infected with COVID-19 develop immunity and are protected after recovery. In addition, there is no evidence available in cancer patients on what constitutes recovery (i.e. clinical recovery, serologic or PCR negativity).

The following provides an overview of recommendations from leading expert groups and health authorities on hospital discharge criteria for confirmed COVID-19 cases. Considering the literature and recommendations from national bodies in countries that have experienced COVID-19 local transmissions, the European Centre for Disease Prevention and Control [23] established the following criteria:

- At least 2 upper respiratory tract samples negative for COVID-19, collected at ≥24-hour intervals are recommended to document COVID-19 clearance.
- For symptomatic patients after the resolution of symptoms, samples should be collected at least 7 days after the onset or after >3 days without fever.
- For asymptomatic COVID-19-infected people, tests to document virus clearance should be taken at a minimum of 14 days after the initial positive test.

The Centers for Disease Control and Prevention [22] established the following criteria as part of the recommended test-based-strategy:

- Resolution of fever without the use of fever-reducing medications, and
- Improvement in respiratory symptoms (e.g., cough, shortness of breath), and
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- Negative results of an COVID-19 molecular assay for detection of COVID-19 RNA from at least 2 consecutive nasopharyngeal swab specimens collected ≥24 hours apart (total of 2 negative specimens)

If testing is not readily available, the Centers for Disease Control and Prevention advised that facilities use the following criteria:

- At least 72 hours have passed since recovery defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath), and
- At least 7 days have passed since symptoms first appeared

Based on available hospital data of infected patients in China, the World Health Organization reported that the median time from onset of COVID-19 to clinical recovery for mild cases is approximately 2 weeks and for patients with severe or critical symptom manifestation it is 3-6 weeks [29].

Alberta Health Services has established that hospitalized patients with a confirmed COVID-19 diagnosis who are immunosuppressed are to be isolated for 14 days from the onset of symptoms and until symptoms have resolved, in addition, they have to have at least 2 consecutive negative nasopharyngeal swabs collected at least 7 days apart [30]. For people in the community known to be sick with COVID-19 Alberta Health Services established that they are to be isolated for a minimum of 10 days (4 additional days for healthcare workers [25]) from the start of symptoms, or until symptoms resolve, whichever is longer [26].

In Alberta, lab testing is available to confirm a suspected diagnosis of COVID-19 for certain populations including those at high risk of community transmission and severe outcomes [26]. As of April 10, 2020, nasopharyngeal and throat swabs are recommended standard for COVID-19 testing [28]. It is important to acknowledge that these tests are sensitive, and can detect prolonged shedding of the virus even when non-viable virus is present. Based on the lack of evidence about the effectiveness of lab testing to define the duration of the infectious period of respiratory viruses, the World Health Organization [32] discourages its routine use to guide infection prevention and control precautions, and suggests that decisions on whether or not a patient has recovered and does not represent an infection threat to others are made on the basis of the patient's clinical condition.

b) What criteria should be used to ensure that patients are well enough to have cancer treatment after COVID-19 infection?

There are currently no accepted guidelines as to when cancer treatment can be safely initiated or reinitiated after a COVID-19 infection. Given that reinfection rates are unknown, the potential effects of further suppressing or augmenting a patient's immune system quickly after a COVID-19 infection must be weighed heavily against the prognosis and risks of delaying treatment. Clinicians will need to decide locally and on a case-by-case basis based on expert judgement.

Kutikov, Weinberg [14] developed the following guidelines based on expert consensus:

- Based on low risk of progression in certain cancers, it may be safe to delay for more than 3 months certain treatments, regardless of age (including surgery and radiation for non-melanoma skin cancer, and treatments for chronic hematologic cancers).
- Based on intermediate risk of progression in other cancers, a delay of approximately 3 months may be acceptable the following settings, particularly for individuals aged 50 and older: 1) surgery for high-risk prostate cancer, colon cancer with low risk for imminent obstruction, low-risk melanoma, 2) radiation for post-resection endometrial cancer and high-risk resected prostate cancer, 3) chemotherapy for advanced breast, colorectal, and lung cancer.
- Given a high risk of progression in certain cancers, no delay is recommended in treatments for under age 70: 1) surgery for ≥2 cm lung mass; colon cancer with imminent obstruction; type 2 endometrial cancer; pancreatic, ovarian, or liver mass(es) suspicious for malignancy; high-risk non-muscle invasive or
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muscle invasive urothelial cancer; 2) radiation for lung cancer; locally advanced rectal cancer; head and neck cancer; 3) chemotherapy for acute leukemia, large cell lymphoma, Hodgkin lymphoma, symptomatic myeloma, and all other non-low-grade hematologic cancers; testicular cancer; small cell lung cancer; most head and neck cancers, except thyroid.

In addition to these guidelines:

The National Institute of Clinical Excellence [24] recommended a delay of at least 3 months for haematopoietic stem cell transplantation, except for patients who have a high risk of disease progression, morbidity or mortality, in which case they suggest deferral until patients no longer show symptoms and have 3 repeated negative PCR tests, at least 1 week apart.

Guckenberger, Belka [21] made practical recommendations to treat patients with lung cancer including postponing the initiation of radiotherapy until the patient becomes asymptomatic and tests negative for COVID-19, and interrupting radiotherapy until the patient becomes asymptomatic and tests negative for COVID-19 in the three cases of non-curative intent radiotherapy. Banna, Curioni-Fontecedro [9] propose a tool to support oncologists and physicians in treatment decision for patients with lung cancer.

The FRANCOGYN group recommended that surgical management of patients with gynecologic cancers should be postponed for at least 15 days [18]. Penel, Bonvalot [20] presented recommendations for sarcoma patients including postponing any treatment at least 15 days after the start of the symptoms and when the patient has recovered. Other tumour groups may have their own tumor-specific recommendations.

Evidence from the primary literature

It is well established that cancer patients are more susceptible to infections than individuals without cancer because of their immunosuppressive state caused by the malignancy and cancer treatments [10,11,33]. There is also extensive literature indicating that cancer patients are at increased risk for serious complications such as pneumonia and hospitalization [3,4,10]. For example, in a retrospective study during the 2009 influenza A (H1N1) virus pandemic, the cancer patient population was at higher incidence of pneumonia (66%) and 30-day mortality (18.5%) compared with the general population [8].

Specific to COVID-19, recent research concluded that cancer patients had more severe symptoms and worse outcomes from COVID-19 than individuals without cancer [4]. Recent data on cancer patients with a COVID-19 diagnosis in China showed an association between severe events related to the COVID-19 infection and having undergone chemotherapy or surgery in the month before diagnosis [4-6,16,17]. In addition, and despite limitations related to the small size of the population, these data revealed two interesting findings. First, that recent use of therapies within 14 days of infection (including chemotherapy, immunotherapy and radiotherapy) was an independent predictor of death or other severe events with a hazard ratio of greater than 4. Second, that there was a high proportion of patients who acquired the infection while already in the hospital [6]. Based on these findings the authors suggested that interrupting cancer treatment in patients with active COVID-19 should be strongly considered. Further, the authors recommended the interruption and postponement of adjuvant chemotherapy and elective surgery for less aggressive cancers, and decreasing dosage of treatments that cause immunosuppression [4,6].

Supporting these recommendations, a simple model developed by Williams, Le Calvez [7] has shown that for chemotherapy the risks of infection-related complications may outweigh the benefits of treatment, particularly for patients with solid tumors, at older ages or with other comorbidities.

For patients undergoing immunotherapy, there is limited evidence and conflicting data. While it has been acknowledged that these patients could gain immunocompetence and potentially benefit from treatment [13], it has also been discussed that they might be at higher risk of complications [11]. In the context of an influenza
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infection treatment decision, some researchers have recommended to consider the particularities of the immunological status of these cancer patients [12].

Evolving Evidence
We acknowledge that the evidence regarding the care and management of individuals that are suspect or confirmed COVID-19 is rapidly evolving. Therefore significant changes in clinical guidelines may occur and impact this rapid review.

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(If applicable) Date of re-assessment:

Authorship & Committee Members
This review was written by Anna Pujadas-Botey and scientifically reviewed by Douglas Stewart (external reviewer), Lynora Saxinger (co-chair), and Charlie Butts (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.
Appendix

Literature Search Details

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 07, 2020

1 exp Coronavirus/ or exp Coronavirus Infections/ or coronaviru*.mp. or "corona virus"*.mp. or ncov*.mp. or n-cov*.mp. or "novel cov".mp. or COVID-19.mp. or COVID-19.mp. or COVID-2019.mp. or COVID2019.mp. or COVID-2019.mp. or SARS-COV-2.mp. or SARS-CoV-2.mp. or SARS-CoV2.mp. or SARS-CoV19.mp. or SARS-COV19.mp. or SARS-CoV-2019.mp. or SARS-CoV-2019.mp. or SARS-CoV-2019.mp. or SARS-CoV-2019.mp. or SARS-CoV-2019.mp. or SARS-CoV-2019.mp. or "severe acute respiratory syndrome cov"2.mp. or "2019 ncv".mp. or "2019ncov".mp. (21600)

2 exp Antineoplastic Agents/ (1085465)
3 exp antineoplastic protocols/ or exp chemoradiotherapy/ or consolidation chemotherapy/ (149499)
4 Chemotherapy, Cancer, Regional Perfusion/ (3739)
5 Induction Chemotherapy/ (2606)
6 (antineoplastic* or chemo* or cytotoxic or radiochemo* or myeloma* or neuroblastoma* or osteosarcoma* or glioma* or adenocarcinoma* or hematological* or hemato-oncological* or haematological* or haematological* or nephroblastom* or immunoradiotherap*).kf.tw.(1080928)

7 or/2-6 (1889979)
8 1 and 7 (961)
9 limit 8 to (English language and yr="2003 -Current") (643)
10 limit 9 to yr="2020 -Current" (25)
11 limit 9 to (guideline or meta analysis or practice guideline or "review" or "systematic review" or systematic reviews as topic) (64)
12 10 or 11 (83)

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antineoplastic* or chemo* or cytotoxic or radiochemo* or myeloma* or neuroblastoma* or osteosarcoma* or glioma* or adenocarcinoma* or hematological* or hemato-oncological* or haematological* or haematological* or nephroblastom* or immunoradiotherap*

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(antineoplastic* or chemo* or cytotoxic or radiochemo* or myeloma* or neuroblastoma* or osteosarcoma* or glioma* or adenocarcinoma* or hematological* or hemato-oncological* or haematological* or haematological* or nephroblastom* or immunoradiotherap*) AND (coronaviru* OR "corona virus" OR ncov* OR n-cov* OR COVID-19 OR COVID19 OR COVID2019 OR SARS-COV-2 OR SARS-CoV-2 OR SARS-CoV2 OR SARS-CoV-19 OR SARS-CoV-19 OR SARS-CoV2019 OR SARS-CoV-2019 OR SARS-CoV-2019 OR "severe acute respiratory syndrome cov"2 OR "severe acute respiratory syndrome coronavirus"* OR "2019 ncov" OR 2019ncov OR Hcov*) OR "clinical recovery from COVID19" OR "recovery from COVID19"

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Reference List


