

COVID-19 Testing in Patients with Cancer: Does One Size Fit All?



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ABSTRACT

The COVID-19 global pandemic has drastically impacted cancer care, posing challenges in treatment and diagnosis. There is increasing evidence that cancer patients, particularly those who have advanced age, significant comorbidities, metastatic disease, and/or are receiving active immunosuppressive therapy may be at higher risk of COVID-19 severe complications. Controlling viral spread from asymptomatic carriers in cancer centers is paramount, and appropriate screening methods need

to be established. Universal testing of asymptomatic cancer patients may be key to ensure safe continuation of treatment and appropriate hospitalized patients cohorting during the pandemic. Here we perform a comprehensive review of the available evidence regarding SARS-CoV-2 testing in asymptomatic cancer patients, and describe the approach adopted at Princess Margaret Cancer Centre (Toronto, Canada) as a core component of COVID-19 control.

Introduction

As the coronavirus disease (COVID-19) pandemic unfolds, there is emerging evidence that patients with cancer are particularly vulnerable to infection and adverse events, with poorer outcomes than the general population (1, 2). In response, cancer centers and physicians around the world are rapidly trying to determine the best strategies to protect patients with cancer from COVID-19. There is an urgent need to gain a broader understanding of risk factors associated with severity and outcome of COVID-19 in patients with cancer, including the risk associated with different types of cancer therapy. In this setting, the issue of routine testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in asymptomatic patients with cancer has been particularly contentious.

Methods of Testing for SARS-CoV-2

Detection of SARS-CoV-2 viral RNA by reverse transcriptase PCR (RT-PCR) remains the current gold-standard for diagnosis. Several protocols for RT-PCR testing have been developed, with different gene targets (3–5). Diagnostic testing using RT-PCR may be performed using nasopharyngeal swab (preferred), other upper respiratory specimens, including throat swabs and saliva, or lower respiratory tract

specimens. The small studies assessing saliva samples require further validation (6–8).

High false-negative rates remain a key issue with RT-PCR testing (9, 10). In China, an early study reported total positivity rate of RT-PCR for throat swab samples at initial presentation to be 30%–60% (11). The timing of RT-PCR testing in relation to symptom onset is likely to be critical, highlighting the utility of repeat testing. Several studies have reported a “turn positive” of nucleic acid detection by RT-PCR test for SARS-CoV-2, with one study demonstrating that 15/60 (21.4%) patients experienced a “turn positive” after two consecutive negative results, which may be related to the false negativity of RT-PCR tests and prolonged nucleic acid conversion (10). As per the World Health Organization (WHO), false-negative result may be related to poor specimen quality, timing of collection (early or late in the infection) inappropriate handling and shipping of specimen or technical reasons (3).

Other testing strategies for SARS-CoV-2

Serology

Serologic testing has the capacity to supplement RT-PCR testing when molecular results are nondiagnostic (Table 1; refs. 12–14). A comprehensive virologic assessment of 9 patients with mild to moderate SARS-CoV-2 infection at a German institution reported that seroconversion was demonstrated in 50% of patients after day 7, and 100% of patients by day 14, with all patients developing neutralizing antibodies (15). Several larger studies from China, using ELISA or lateral flow assays, have similarly reported that the majority of patients show seroconversion by 14 days after onset of the infection, while detection of SARS-CoV-2 by quantitative RT-PCR starts to decline after day 5 (12–15). The Infectious Diseases Society of America has cautioned that antibody tests should not be used as a standalone test for diagnosis (16). It remains unclear how the antibody response to SARS-CoV-2 evolves in infected patients, whether the generated antibodies are protective, and whether the protective response is sustained. In addition, there is no universal standard for reporting, and cross-reactivity with other known coronaviruses may be a significant issue.

Point-of-care testing

Point-of-care assays are obviously attractive for their rapidity of results; however, these assays require further validation, as published studies involve only small numbers of patients. Sample-to-answer

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Translational Relevance

Universal baseline SARS-CoV-2 testing in patients with cancer is important to complete oncologic treatments safely during the COVID-19 pandemic, and toward ensuring the continuation of systemic therapy, radiation, and surgical procedures. This measure is also key to warrant that cancer patients' outcomes do not significantly worsen during the pandemic. The identification of asymptomatic carriers can help adjust oncologic therapy, reduce viral shedding from asymptomatic carriers and provide a safer environment for treatment continuity. In this review, we propose a model of care for universal SARS-CoV-2 testing to be performed on all patients with cancer receiving active treatment or requiring admission. This model of care has been adopted in Princess Margaret Cancer Centre and the Province of Ontario (Canada). In addition, this policy has been foundational to the development of translational trial protocols assessing SARS-CoV-2 testing in our center (NCT04373005).

molecular diagnostic platforms have been granted FDA emergency use authorization, but there is concern that they are limited in analytic and clinical performance (17, 18). Other assays include a reverse transcription-loop-mediated isothermal amplification method (19), and antibody-based rapid serologic testing (20). On the basis of current evidence, WHO recommends the point-of-care immunodiagnostic tests are used only in research settings.

Imaging

Recommendations for imaging continue to evolve as the pandemic progresses. Radiologic assessment may be considered adjunctive to confirming the diagnosis in patients where clinical suspicion is high, and where molecular testing is nondiagnostic. While the American College of Radiology, for example, has discouraged the use of imaging for COVID-19 diagnosis, a panel of radiologists and pulmonologists has subsequently suggested that chest imaging may be indicated in patients with worsening respiratory status, and could potentially be used to triage suspected patients (21, 22).

The Challenge of Detecting Asymptomatic Carriers

Globally, guidelines for the general population recommend testing in people perceived to be at higher risk based on symptomatology and exposure history but not asymptomatic individuals (23, 24). This approach is potentially suboptimal in protecting a vulnerable cancer population, as transmission from asymptomatic carriers represents a serious risk.

Preliminary evidence from exported COVID-19 cases suggests that transmission during the early phase of the illness appears to contribute to overall transmission (25). Viral shedding patterns are not yet well understood, and further investigations are needed to better understand the timing, compartmentalization, and quantity of viral shedding to inform optimal specimen collection (3). It is estimated that the mean incubation period for COVID-19 could be between 3 to 6 days (Table 2; refs. 26–28). A prospective study in China detected positive SARS-

Table 1. Summary of published serologic-based studies for COVID-19 testing.

Reference	Testing method	Study population	Results
Guo et al. (12)	ELISA based on SARS-CoV-2 viral nucleocapsid protein; IgM Ab, IgA Ab, IgG Ab	208 plasma samples from 82 confirmed and 58 probable COVID-19 cases	The combination of IgM ELISA plus PCR detected 98.6% of cases versus 51.9% with a single PCR. During the first 5.5 days, PCR had higher positivity rate than IgM; the reverse was true after day 5.5.
Zhao et al. (13)	Total Ab, IgM Ab, IgG Ab to SARS-CoV-2	Serial blood samples from 173 patients with PCR-confirmed COVID-19	In samples collected during the first 7 days after illness onset, positive rates were 66.7% for PCR and 38.3% for antibody assays. During the second week after illness onset, positive rates were 54.0% for PCR and 89.6% for antibody assays. The combined use of PCR and antibody testing improved identification of positivity through various phases of illness. A strong correlation was found between clinical severity and antibody titer more than 2 weeks after illness onset. Total antibody was more sensitive than IgM or IgG antibody.
Li et al. (14)	Lateral flow immunoassay detects IgM and IgG Ab simultaneously from finger-prick blood, serum, plasma.	Plasma from 397 PCR-confirmed COVID-19 patients and on 128 negative patients from six provinces in China.	Turn-around time 15 minutes. Overall sensitivity was 88.7% and specificity was 90.6%.
Wölfel et al. (15)	IgG and IgM IFA using cells expressing the spike protein of SARS-CoV-2 and a virus neutralization assay.	Virologic analysis of 9 patients diagnosed by RT-PCR in Germany.	Seroconversion in 50% of patients occurred by day 7, and in all by day 14. No viruses were isolated after day 7. All patients showed detectable neutralizing antibodies. The titers did not suggest close correlation with clinical courses. Authors recommend that ELISA tests should be developed as screening test, as IFA is a labor-extensive method.

Abbreviations: Ab, antibody; COVID-19, coronavirus disease 2019; IFA, immunofluorescence; IgA Ab, immunoglobulin A antibody; IgG Ab, immunoglobulin G antibody; IgM Ab, immunoglobulin M antibody; RT-PCR, reverse transcriptase PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Table 2. Studies with published data on mean incubation period for COVID-19.

Reference	Population	Incubation period
Li et al. (26)	Wuhan (<i>n</i> = 425)	Mean 5.2 days (95% CI 4.1–7.0), 95th percentile 12.5 days (95% CI 9.2–18)
Backer et al. (27)	Infected travelers from Wuhan (<i>n</i> = 88)	Mean 6.4 days (95% CI 5.6–7.7)
Guan et al. (28)	China (<i>n</i> = 1,099)	Mean 3.0 days (up to 24 days)

CoV-2 IgM in a family cluster involving 2 patients and four close contacts, confirming the presence of antibodies in asymptomatic infection (12).

The effectiveness of isolation and symptom-based screening methods depends on the proportion of transmission that occurs before symptom onset. It has become apparent that asymptomatic and mild cases are common in COVID-19 (29). Patients with asymptomatic or mild disease manifestations would be missed even if a more sensitive symptom-based surveillance system were in place, and these patients might spread the disease silently (30). A study on universal screening on 215 patients admitted for delivery in New York showed that asymptomatic carriers were common (31). In fact, 13.5% of women admitted for delivery tested positive being asymptomatic (31).

Risk Assessment in Patients with Cancer

Patients with cancer are immunosuppressed, both due to their underlying malignancy, as well as their anti-cancer therapy, including chemotherapy, radiation, or surgery, and therefore can be prone to infection. Several studies have suggested an increased risk of infection or severe outcomes in patients with cancer (32–34). A meta-analysis including 1,558 patients with COVID-19 from six Chinese studies showed no correlation between malignancy and increased risk of COVID-19 aggravation (35). However, only 50 patients with cancer were included in the study, and it was not reported whether the patients had an active malignancy or active treatment.

Further data is needed in regards to specific cancer-related risk of infection. A cohort study by Kuderer and colleagues included 928 patients with active or previous malignancy and confirmed COVID-19, showing no significant correlation of type of cancer or anticancer therapy with mortality (36). A multicenter study compared 105 cancer patients with 536 age-matched noncancer patients with COVID-19 in China (37). Patients with hematologic cancer, lung, or stage IV metastatic cancer had the highest frequency of severe events, while patients with nonmetastatic cancer had similar outcomes to those patients without cancer (37).

Using statistical modeling, Williams and colleagues integrated data on SARS-CoV-2 infection obtained from the Chinese Center for Disease Control and Prevention, statistics from Italian public health authorities, and a report on SARS-CoV-2 infection on board a cruise ship with data from seasonal influenza outbreaks, to estimate the case fatality rate in patients with cancer and SARS-CoV-2 infection (2). The case fatality rate was calculated by age group, with and without chemotherapy, and was found to be 3.1% for patients with cancer not receiving chemotherapy, and 7.6% for those on active chemotherapy. Age was also found to be a significant risk factor for death. The authors established a model that balances the overall survival benefit from the chemotherapy against the predicted risk of death from SARS-CoV-2 infection. This suggests that the overall 5% increase in risk of death if infected by SARS-CoV-2 may be greater than or equal to

the benefit of most adjuvant chemotherapies for adults with solid tumors.

When considering the data presented above, heterogeneity of patient populations, healthcare systems, as well as differences in healthcare provision and case reporting need to be taken into account. Precise estimates of risk are therefore difficult to determine, but there appears to be consistent evidence that patients with cancer are at an increased risk of severe COVID-19. Hence, the implementation of additional measures in the care of these patients should be considered to protect this vulnerable patient population.

Risk factors contributing to infection with SARS-CoV-2 in patients with cancer

The risk factors for COVID-19 in patients with cancer have largely been extrapolated from data reported in immunocompromised patient populations affected by well-known community-acquired respiratory viruses such as influenza and respiratory syncytial viruses. These include pulmonary disease, cardiac disease, neurologic and neurodevelopmental conditions, hematologic, endocrine, renal, hepatic or metabolic disorders, extreme obesity (body mass index of ≥ 40 kg/m²), and immunosuppression due to disease or medication (38). Emerging studies on SARS-CoV-2 infection in patients with cancer support a strong relationship of severity with older age, and to a lesser extent (mainly due to small sample size), with chronic comorbid medical conditions (1, 39, 40).

In the cohort study by Kuderer and colleagues, an increased risk of 30-day mortality was identified with increased age [per 10 years; OR, 1.84; 95% CI, 1.53–2.21], male sex (OR 1.63; 95% CI, 1.07–2.48), smoking status (OR 1.60; 95% CI, 1.03–2.47), number of comorbidities (two vs. none: 4.50; 95% CI, 1.33–15.28), Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2 (OR: 3.89; 95% CI, 2.11–7.18), active cancer (OR 5.20; 95% CI, 2.77–9.77; ref. 36). Race, ethnicity, obesity, and recent surgery were not associated with mortality (36).

A meta-analysis including the general population suggested that hypertension (OR 2.29; 95% CI, 1.69–3.10), diabetes (OR 2.47; 95% CI, 1.67–3.66), chronic obstructive pulmonary disease (OR 5.97; 95% CI, 2.49–14.29), cardiovascular disease (OR 2.93; 95% CI, 1.73–4.96), and cerebrovascular disease (OR 3.89; 95% CI, 1.64–9.22) were independent risk factors (35). Another meta-analysis including 2,282 cases showed that patients with lymphopenia had an increased risk of severe COVID-19 (OR 2.99; 95% CI, 1.31–8.82; ref. 41).

Defining Treatment Priorities and Impact of SARS-CoV-2 Test Result in Patient Care

Establishing cancer treatment priorities in the context of COVID-19 pandemic is critical, and needs to be balanced against the likelihood of benefit from treatment. In the Province of Ontario, Cancer Care Ontario (the government agency responsible for cancer care and

Table 3. High priority testing characteristics in asymptomatic patients with cancer, especially in the event of testing limitations, as per the Ontario Ministry of Health.

High priority testing characteristics
Patients arriving from long-term care facilities, retirement homes, group homes, correction facilities.
Patients with a significant contact with a person with COVID-19, or a household contact with symptoms and not able to defer therapy for 14 days.
Inpatients
Outpatients on radiation/systemic therapy with a risk of immunosuppression from the treatment or underlying disease state and one or more high-risk characteristics:
<ul style="list-style-type: none"> • Age ≥ 60 years • Performance status ≥ 2. • Comorbid conditions (cardiovascular, COPD, diabetes, renal failure) or lymphopenia • Prolonged or severe immunosuppressive regimens • Significant smoking history • Lung tissue in the radiation treatment volume

delivery), has recommended the establishment of three categories of treatment priority in patients with cancer: (A) patients who are deemed critical and require immediate services/treatment; such patients are unstable, have unbearable suffering and/or immediately life-threatening complications (i.e., rapidly progressing tumors, spinal cord compression); (B) patients who require services/treatment, but whose situation is not critical; and (C) patients who are generally healthy, whose condition is deemed as non-life threatening where treatment can be delayed without anticipated change in outcome (42).

In individuals considered to be in priority C, clinicians will generally consider treatment delay during the pandemic. Having a positive COVID-19 result in asymptomatic or mildly symptomatic patients, would likely impact the care of patients in scenarios A and B. Baseline testing for SARS-CoV-2 allows the physician to improve risk stratification, and thereby tailor treatment decision making at the initiation of new systemic therapy. For example, in patients who require urgent oncologic therapy for rapidly progressing tumors, such as certain gestational trophoblastic neoplasms, or germ cell tumors (priority A), a positive COVID-19 result would likely impact patient monitoring, treatment intensity and possibly the administration of supportive therapy such as G-CSF. The determination of a baseline positive test would also help to establish stricter infection control measures for hospital personnel caring for that patient, and ensure treatment administration in a COVID-19 cohorted area within a hospital ward or chemo-daycare unit (43). In patients with cancer defined as priority B (i.e., a solid tumor in noncritical situation), a positive COVID-19 test would likely lead to a delay of treatment with more intensive monitoring.

Proposal of A Model of Care for SARS-Cov-2 Testing in Asymptomatic Patients with Cancer

Patients with cancer, and especially those on immunosuppressive treatment are considered more vulnerable to viral infection and nosocomial transmission. Data supports the testing of SARS-CoV-2 prior to systemic therapy, radiation, and surgery, as infected patients may be asymptomatic, mildly symptomatic, or may not report symptoms from fear of being denied treatment (Fig. 1). Until further data

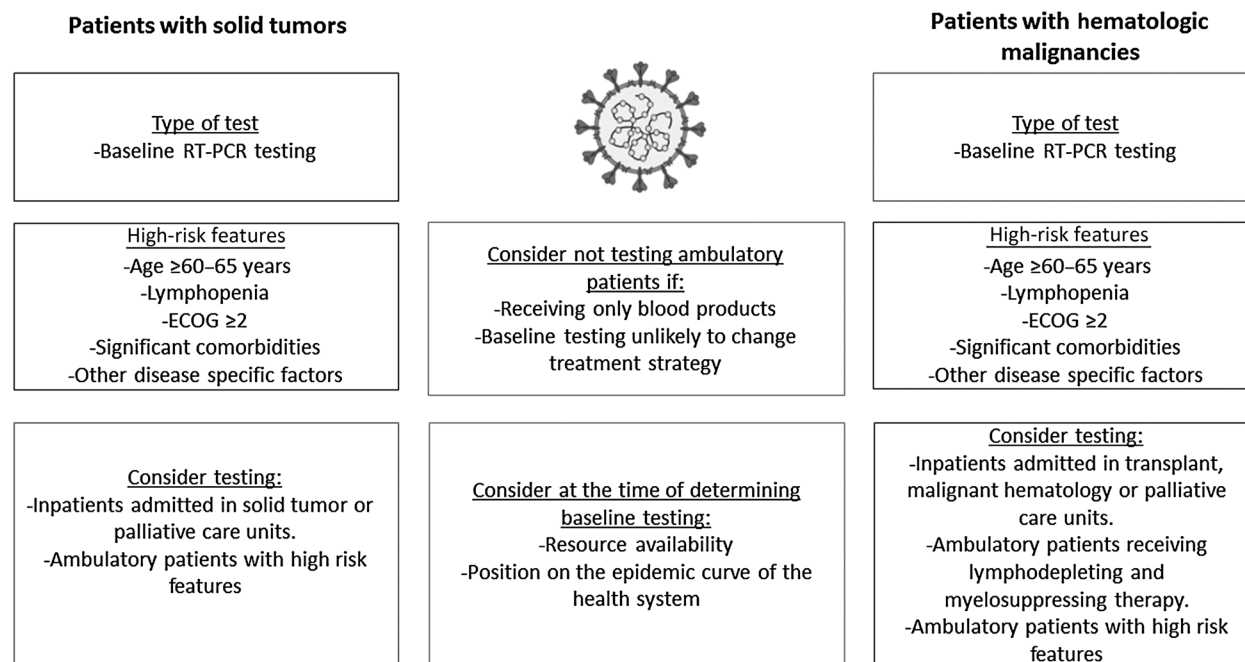


Figure 1. Proposal of SARS-CoV-2 testing recommendations in asymptomatic patients with cancer during COVID-19 pandemic.

emerges, our approach is that age, ECOG status ≥ 2 , significant comorbidities and lymphopenia ($<0.7 \times 10^9/L$), should be considered as high-risk characteristics.

Baseline testing should be considered in all inpatient units of Cancer Centers, as this allows patient cohorting. In our cancer center, a single swab is obtained on days 0 and 7 from admission. Ambulatory patients considered at risk, or those who are receiving immunosuppressive therapies in whom knowledge of COVID-19 infection status would impact on the decision to treat or defer, or on treatment intensity. In our center, all patients receiving systemic therapy, radiation, and all transplant and CAR-T patients and/or donors are being tested. In addition, all scheduled surgical patients are tested 24–48 hours presurgery, then advised to self-isolate until surgery. Guidelines will need to be updated as new data emerges.

The Ontario (Canada) provincial Ministry of Health guidelines recommend baseline testing to patients with asymptomatic cancer prior to starting on immunosuppressive cancer treatment (44). **Table 3** summarizes the testing priority in the case of limited testing capacity. Guidelines recommend that patients booked for radiation simulation, systemic therapy, and hematopoietic cell therapy should be tested within 24–48 hours prior to treatment.

Laboratories may need to develop novel systems and infrastructure for sample processing and results notification, and must be adequately prepared for the safe handling of an influx of potential COVID-19–positive specimens (3, 45). As knowledge evolves, and if immune protection is conferred, serologic testing may allow easier decision making in the future.

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Conclusion

In developing this screening policy, primary consideration was focused on protecting the safety of our patients during this pandemic, acknowledging that patients with cancer represent a uniquely vulnerable population. Secondary consideration was given to the technical aspects of testing, community incidence of infection, and pragmatic considerations such as health service testing capacity, and follow up of results. In situations where resources are limited, testing patients with symptoms and exposure to COVID-19 will need to be prioritized. As a best practice recommendation, we propose that in the context of confirmed cases in the centre, baseline testing prior to initiating systemic or radiotherapy, or upon admission should be considered in asymptomatic or mildly symptomatic patients, especially those with high-risk features. These policies will evolve as more data becomes available, and as we continue to adapt in response to new evidence during this current pandemic.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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