

The Emirates Oncology Task Force Clinical Practice Guideline on Screening for SARS-CoV-2 in Asymptomatic Adult Cancer Patients Prior to Anti-Cancer Therapy

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ABSTRACT

The Emirates Oncology Task Force Clinical Practice Guideline on Screening for SARS-CoV-2 in Asymptomatic Adult Cancer Patients Prior to Anti-Cancer Therapy

Introduction: Cancer care during this pandemic is challenging given the competing risks of death from cancer versus death or serious complications from SARS- CoV-2 infection, and the likely higher lethality of COVID-19 in immunocompromised patients. Question remains on serial screening for SARS-CoV-2 in asymptomatic adult cancer patients prior to anti-cancer therapy during the COVID-19 pandemic.

Methods: We conducted a systematic review to formulate a consensus statement to guide the practising oncologists.

Results: Most of the current guidelines recommends RT-PCR SARS-CoV-2 testing of asymptomatic patients prior to initiating and during the anti-cancer therapy despite the lack of robust evidence. We suggested the following: If screening is indicated in adult cancer patients, we recommend using RT-PCR over serum antibody or serum antigen for adult cancer patients; we also recommend assessing the risk of exposure to and infection from SARS-CoV-2 prior to each anti-cancer cycle, to consider SARS-CoV-2 in asymptomatic adult cancer patients prior to anti-cancer therapy in high risk groups : highly cytotoxic chemotherapy with potential profound neutropenia based on the physician's risk assessment of the chemotherapy , stem cell transplantation. For asymptomatic intermediate-high risk cancer patients, we suggest performing RT-PCR 48-72 hours prior to initiating any anti-cancer therapy. For asymptomatic low-risk cancer patients, we suggest not to routinely screen prior to initiating any anti-cancer therapy (weak recommendation, low quality evidence).

Conclusion: SARS-CoV-2 screening might be indicated with higher certainty to certain cancer risk groups. There remains a need for prospective trials to assess this intervention, and the outcome of such intervention. Current recommendations may change based on new and emerging evidence.

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has rapidly spread globally since being identified as a public health

emergency of major international concern and has now been declared a pandemic by the World Health Organization (WHO) [1]. The COVID pandemic has disrupted clinical care across the world, and presents unique challenges for oncology patients, who must frequently visit the hospital for treatment and disease surveillance. Several factors increase the risk of infection, and cancer patients commonly have multiple risk factors [1,2].

Delivering care for patients with cancer during this pandemic is challenging given the competing risks of death from cancer versus death or serious complications from SARS-CoV-2, and the likely higher lethality of COVID-19 in immunocompromised patients [2,3]. The aim of this guideline is to systematically summarize the available evidence and issue recommendations to guide oncologists regarding screening for COVID-19.

Methods

Panel Selection

The chair of the guideline nominated panel members based on their clinical and academic expertise in cancer management. The panel included experts in guideline development, medical oncology, radiation oncology, surgical oncology and patients' representative. All the authors have no affiliations that might represent a conflict of interest or that might directly or indirectly influence the content of this article.

Conflict of Interest Management

All panel members completed the WHO conflict of interest disclosure forms. The development of this guideline did not include any industry input, funding, financial, or non-financial contribution. No member of the guideline panel received honoraria or remuneration for any role in the guideline development process.

Guideline Scope

This guideline provides recommendations to support the management adult cancer patients during COVID-19 pandemic. The target users of this guideline are oncologists, hematologists, allied health professionals, and policymakers involved in the care of cancer patients.

Questions

The guideline panel addressed the following clinical questions:

1. Should we recommend serial screening for SARS-CoV-2 in asymptomatic adult cancer patients prior to anti-cancer therapy?
2. When screening for SARS-CoV-2 is indicated, should we recommend using Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) versus serum antibody or serum antigen testing?

Systematic Review

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework [4]. We searched Pubmed, Embase, Google scholar, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Elsevier's Scopus from Nov 1st 2019 to July 30th 2020, using the terms 'COVID19', 'COVID-19', 'SARS-CoV19', 'SARS-CoV-19', 'cancer', 'Malignancy', 'Neoplasm', 'Asymptomatic', 'Screening', 'Anti-Cancer', 'Chemotherapy', 'Immunotherapy', 'Targeted therapy', 'PCR', 'Antibody', 'Antigen', and 'Serial Screening'. We also searched major international oncology and infectious diseases societies websites to identify relevant guidelines addressing the COVID-19 pandemic. These included the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society for

Medical Oncology (ESMO), The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines, The American Society for Transplantation and Cellular Therapy (ASTCT), The British society of blood and marrow transplantation and cellular therapy (BSBMT&CT), the UK National Cancer Research Institute Groups (NCRI) -AML Working Party (NCRI-AML), European Hematology Association (EHA), and Infectious Diseases Society of America (IDSA) (Figure 1).

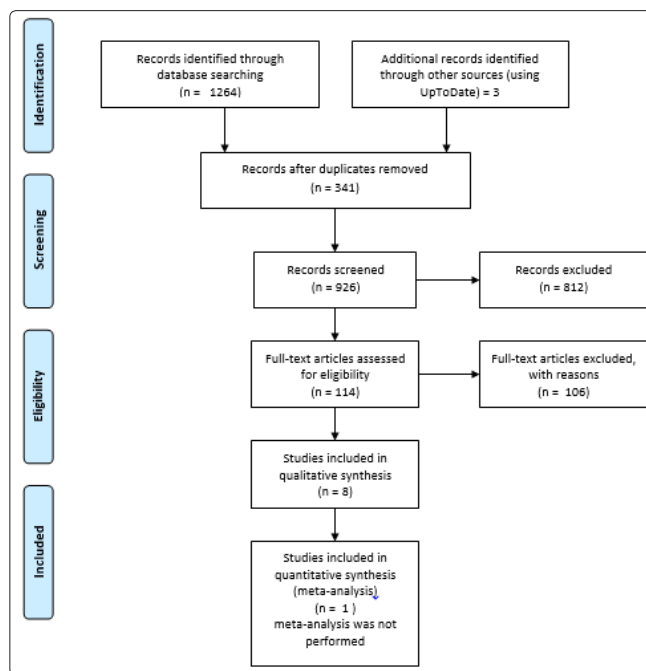


Figure 1: PRISMA flow diagram of the systematic review article selection process

We included peer reviewed studies and societies guidelines in English language only which evaluated SARS-CoV-2 testing strategies for SARS-CoV-2 of asymptomatic adults prior to initiating anti-cancer therapy (i.e. such as chemotherapy, immunotherapy, targeted-therapy, surgery or radiation therapy for cancer patients). We excluded preprint, duplicate articles and case reports.

Two reviewers (H.O.A and A.S.A) screened titles and abstracts, and assessed full-text manuscripts. Disagreements were resolved by a third reviewer SA.

GRADEing the Evidence

The evidence was presented to all authors and the relative strength of evidence, limitations, magnitude of benefit of testing, and cost was addressed in a panel discussion. We reached a consensus regarding the recommendation for screening of asymptomatic cancer patients prior to anticancer therapy.

Summary of the Evidence

Only one prospective cohort study and 7 consensus guidelines were identified addressing RT-PCR for SARS-CoV-2 testing. Therefore, it was not possible to summarize any data quantitatively. There were no studies addressing antibody versus antigen testing for SARS-CoV-2 in asymptomatic cancer patients.

The only cohort study which was conducted by this first author's group from Alzahra Hospital Dubai, United Arab Emirates, where 85 asymptomatic adult cancer patients were enrolled.

All patients underwent a RT-PCR for SARS-CoV-2. RT-PCR was repeated until two consecutive negative results were achieved. Screening RT-PCR was found to be positive in 7 (8.24%) out of the asymptomatic 85 patients, five of them (71.4%) on systemic therapy and two who had not yet initiated therapy. All RT-PCR positive patients eventually became symptomatic: five with mild symptoms and two with severe symptoms, requiring intensive care unit admission. The patients with mild symptoms resumed therapy after virologic clearance (median 18 days). This small cohort had some limitations, such as: single center experience and no control group [5].

International Societies Guidelines

Seven consensus guidelines addressing the use of RT-PCR for SARS-CoV-2 in asymptomatic cancer patients were identified. None of the guidelines included specific recommendations for antibody versus antigen testing. The recommendations vary based on the cancer population (Table 1). The NCCN guidelines do not recommend routine testing for all asymptomatic patients prior to initiating or during the anti-cancer therapy. The only recommendations were for hematologic malignancies and stem cell transplant: “testing for SARS-CoV-2 should be considered in asymptomatic patients before receiving chemotherapy that will result in significant and prolonged immunosuppression” [6].

Table 1: International Societies guidelines Recommendations

Guideline	Recommendation
ASTCT	“In the case of a patient in a community with widespread disease, “all HCT and cellular therapy candidates should undergo screening for SARS-CoV-2 infection by PCR in respiratory specimens at the time of initial evaluation and 2 days prior to conditioning/lymphodepletion, regardless of the presence of symptoms, if testing is available”
ASCO	After considering availability of tests and laboratory capacity: (1) asymptomatic new patients should be tested for SARS-CoV-2 48-72h prior to initiating treatment with cytotoxic chemotherapy, stem cell transplantation, long-acting biologic therapy, cellular immunotherapy or high-dose corticosteroids (2) screening 48-72h prior to each new cycle of treatment with a standardized questionnaire
BSBMT&CT	“As yet there are no recommendations for the screening of asymptomatic transplant recipients pre-transplantation. Ideally all patients should be screened before starting conditioning, as there is an asymptomatic period screening should be repeated at least twice, 1 week apart, but practice may vary between institutions. However, it would be appropriate to screen transplant patients prior to the start of conditioning if they have a history of recent contact with symptomatic individuals (travel to high-risk countries is rapidly becoming a redundant screening tool)”
EHA	“Testing should be performed in all newly diagnosed AML patients, but also at the start of the next treatment cycle. Serologic testing should be included if possible, in particular in RNA-positive patients.”, No recommendation regarding asymptomatic screening for CML or CLL were provided.
ESMO	(1) SARS-CoV-2 RT-PCR testing should be proposed to all patients undergoing chemotherapy or immunotherapy and ideally before each treatment cycle; If availability of tests is limited, RT-PCR should be offered only for symptomatic patients (2) serology should be offered to all cancer patients. If not available, limit tests to all patients undergoing chemotherapy or immunotherapy or any other active anti-cancer treatment
IDSA	(1) SARS-CoV-2 testing asymptomatic patients before immunosuppressive procedures (i.e., cytotoxic chemotherapy, solid organ or stem cell transplantation, long acting biologic therapy, cellular immunotherapy or high-dose corticosteroids) regardless of known exposure to COVID-19, 48-72h prior to treatment initiation; (2) screening with a standardized questionnaire for symptoms and exposure should be performed in between hospital visits.
NCCN	(1) Do not recommend routine testing for all asymptomatic patients prior to initiating or during the anti-cancer therapy. (2) For hematologic malignancies and stem cell transplant: testing for SARS-CoV-2 should be considered asymptomatic patients before receiving chemotherapy that will result in significant and prolonged immunosuppression.
NCRI-AML	“Recommended all patients should be screened for COVID-19 before initiation of induction or consolidation chemotherapy. If positive, therapy should be delayed if possible until resolution of symptoms (if present) and PCR negativity. Recommendations for the management of patients with AML during the COVID19 outbreak: a statement from the NCRI AML Working Party”
Abbreviations: ASTCT = The American Society for Transplantation and Cellular Therapy, ASCO= American Society of Clinical Oncology; BSBMT&CT= The British society of blood and marrow transplantation and cellular therapy ,ESMO= European Society for Medical Oncology; EHA = European Hematology Association , IDSA= Infectious Diseases Society of America; NCCN= National Comprehensive Cancer Network , NCRI-AML = UK National Cancer Research Institute Groups (NCRI) - AML Working Party (NCRI-AML)	

All other international cancer and hematology organizations identified in this systematic review recommended SARS-CoV-2 screening prior to initiating and during the anti-cancer therapy [7-9]. ASCO advised “after considering availability of tests and laboratory capacity: (1) asymptomatic new patients should be tested for SARS-CoV-2 48-72 hours prior to initiating treatment with cytotoxic chemotherapy, stem cell transplantation, long-acting biologic therapy, cellular immunotherapy or high-dose corticosteroids; (2) screening 48-72 hours prior to each new cycle of treatment with a standardized questionnaire” [7].

The ESMO statement recommended “(1) SARS-CoV-2 RT-PCR testing should be proposed to all patients undergoing chemotherapy or immunotherapy and ideally before each treatment cycle; If availability of tests is limited, RT-PCR should be offered only for symptomatic patients; (2) Serology should be offered to all cancer patients. If not available, limit tests to all patients undergoing chemotherapy or immunotherapy or any other active anti-cancer treatment” [8]. ASTCT recommended “In the case of a patient in a community with widespread disease,” all HCT and cellular therapy candidates should undergo screening for SARS-CoV-2 infection by PCR in respiratory specimens at the time of initial evaluation and 2 days prior to conditioning/lymphodepletion, regardless of the presence of symptoms, if testing is available” [10].

BSBMT&CT commented “As yet there are no recommendations for the screening of asymptomatic transplant recipients pre-transplantation. Ideally all patients should be screened before starting conditioning, as there is an asymptomatic period screening should be repeated at least twice, 1 week apart, but practice may vary between institutions. However, it would be appropriate to screen transplant patients prior to the start of conditioning if they have a history of recent contact with symptomatic individuals (travel to high risk countries is rapidly becoming a redundant screening tool)” [11]. NCRI AML Working Party (Version 4.0 dated 16.06.2020) recommended all patients should be screened for COVID-19 before initiation of induction or consolidation chemotherapy. If positive, therapy should be delayed if possible until resolution of symptoms (if present) and PCR negativity. Recommendations for the management of patients with AML during the COVID19 outbreak: a statement from the NCRI AML Working Party [12].

The EHA published specific recommendations for each malignant hematology condition including AML “Testing should be performed in all newly diagnosed AML patients, but also at the start of the next treatment cycle. Serologic testing should be included if possible, in particular in RNA-positive patients”, No recommendation regarding asymptomatic screening for CML or CLL were provided [13]. And IDSA recommended “(1) SARS-CoV-2 testing of asymptomatic patients before immunosuppressive procedures (i.e., cytotoxic chemotherapy, solid organ or stem

cell transplantation, long-acting biologic therapy, cellular immunotherapy or high-dose corticosteroids) regardless of known exposure to COVID-19, 48-72h prior to treatment initiation; (2) screening with a standardized questionnaire for symptoms and exposure should be performed in between hospital visits [9].

Patients’ Values and Preferences

We included 1 patient representative on the panel. We also conducted an online survey for 10 adults’ patients who are actively receiving anti-cancer therapy during this pandemic. 9 out of the 10 patients expressed their acceptance of SARS-CoV-2 testing prior to each anti-cancer therapy as this provided them with safety net to avoid severe complications from SARS-CoV-2 if they were asymptomatic and received anti-cancer therapy. All patients expressed their concern about the cost of the testing as currently not covered by insurance. All patients all expressed their discomfort from the nasopharyngeal swab procedure to collect the sample. Some patients expressed their interest to have the test in other ways than the nasopharyngeal swab e.g blood or saliva sample if available in the future.

The Emirates Oncology Task Force Recommendations

The Emirates Oncology Task force committee has evaluated the above evidence and given the potential benefits of screening for SARS-CoV-2 in asymptomatic adult cancer patients prior to initiating anti-cancer therapy albeit lack of strong evidence to support universal SARS-CoV-2 RT-PCR screening (Figure 2).

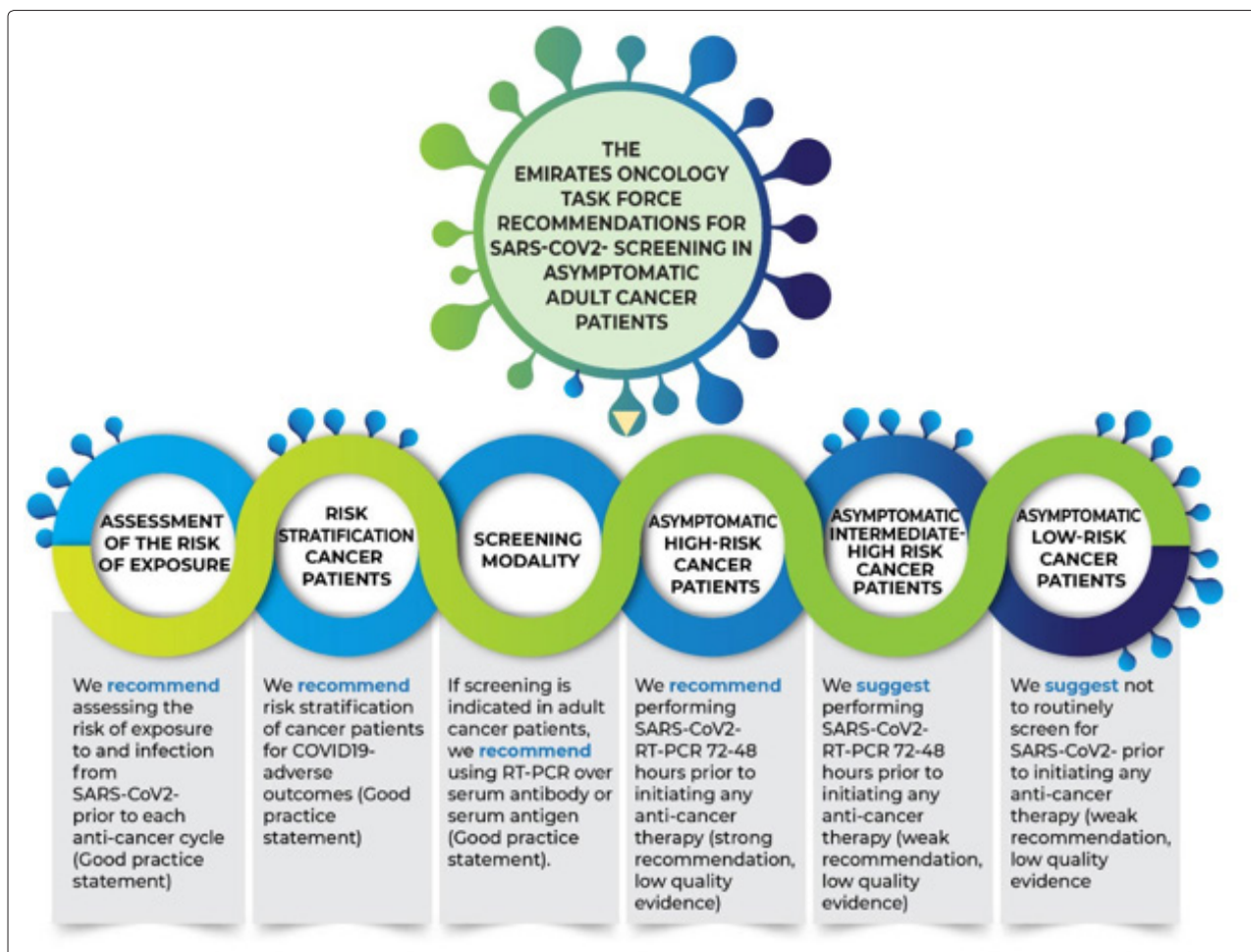


Figure 2: The Emirates Oncology Taskforce Clinical Practice Guideline on Screening for SARS-CoV-2 in Asymptomatic Adult Cancer Patients Prior to Anti-Cancer Therapy

1. For adult cancer patients; we recommend assessing the risk of exposure to and infection from SARS-CoV-2 prior to each anti-cancer cycle (Good practice statement).
Remark: Assessment using telemedicine should be completed 48-72 hours prior to each visit or treatment (systemic therapy, surgery, and/or radiation fraction) using a standardized questionnaire for symptoms of COVID-19 [3].
2. We recommend risk stratification of cancer patients for COVID-19 adverse outcomes (Good practice statement).
Remark: High-risk group includes: Patients receiving highly cytotoxic chemotherapy with potential profound neutropenia based on the physician's risk assessment, stem cell transplantation and cellular immunotherapy. Intermediate to high-risk group includes: older patients > 65 years of age, poor performance status (ECOG > 1), lung cancer, and multiple comorbidities. For low risk we do not recommend routine screening rather discussion about risk and benefit with patients about the screening is preferred (Good practice statement).
3. If screening is indicated in adult cancer patients, we recommend using RT-PCR over serum antibody or serum antigen (Good practice statement).
4. For asymptomatic high-risk cancer patients, we recommend performing SARS-CoV-2 RT-PCR 48-72 hours prior to initiating any anti-cancer therapy (strong recommendation, low quality evidence).
5. For asymptomatic intermediate-high risk cancer patients, we suggest performing SARS-CoV-2 RT-PCR 48-72 hours prior to initiating any anti-cancer therapy (weak recommendation, low quality evidence).
6. For asymptomatic low-risk cancer patients, we suggest not to routinely screen for SARS-CoV-2 prior to initiating any anti-cancer therapy (weak recommendation, low quality evidence).
Remarks: The pros and cons of not screening should always be discussed with the patients, and shared decision making should be considered.

Discussion

Cancer patients may have a higher risk of severe events and unfavorable outcomes in the setting of COVID-19 [1]. It is imperative that oncology health care providers continue to evaluate the best approach to testing to ensure continuity and safety of care for this vulnerable patient population. Especially in the setting of immunosuppressive procedures such as cytotoxic chemotherapy, solid organ or stem cell transplantation, long-acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids [3]. The question regarding the screening of asymptomatic cancer patients prior to anti-cancer therapy is an ongoing debate faced by cancer care providers worldwide. This issue was first raised in early cohort studies which reported an increase in morbidity and mortality in cancer patients who were exposed to anticancer therapy [9,14]. Yet this link has not been consistent in all studies [9,15].

In a recent analysis of international COVID-19 and Cancer Consortium registry data on over 900 patients with active or previous malignancy who had confirmed SARS-CoV-2 infection over a one-month period, the use of anticancer therapy within four weeks of infection was not associated with higher 30-day mortality rates [16]. In another UK study, cancer patients on cytotoxic chemotherapy or other anticancer treatment were not at an increased risk of mortality from COVID-19 disease compared with those not on active treatment [15,16]. In contrast a French study found that patients received chemotherapy in the last 3 months had higher morbidity and mortality from COVID-19 infection [17].

Our systematic review identified one study which was a cohort study (Level 3 evidence) and the remaining were expert consensus opinions in international society guidelines (Level 5). Our systematic review did not demonstrate sufficient evidence to support routine testing for SARS-CoV-2 prior to initiating or during anti-cancer therapy, even though this practice was uniformly recommended in most of the included publications. There are limitations that should be considered when interpreting the results of this review. One of the major limitations is the recent nature/timing of this pandemic. The virus itself and its clinical course remain incompletely understood. There has not been sufficient time to conduct rigorous clinical trials. Arguments against routine screening include the lack of Level 1 or 2 evidence to support the recommendation, the possibility of false negative results associated with the RT-PCR tests, the additional expense for cancer patients, and manpower burden on the healthcare system [15,18].

However, it is difficult to deny the obvious benefit to cancer patients if an infection were identified prior to the initiation of the anti-cancer therapy. It would additionally serve to protect health care providers from potentially being exposed to SARS-CoV-2 while providing care to these patients.

Conclusion

Our systematic review has demonstrated that most of the current guidelines recommend RT-PCR SARS-CoV-2 testing of asymptomatic patients prior to initiating and during the anti-cancer therapy despite the lack of robust evidence. The recommendations are largely based on the expert opinions of the members of the committees. Given the potential benefit of serial screening for SARS-CoV-2 in asymptomatic adult cancer patients prior to anti-cancer therapy during the COVID-19 pandemic and to avoid potential COVID-19 severe morbidity and mortality the Emirates Oncology Task Force Committee suggests to consider SARS-CoV-2 in asymptomatic adult cancer patients prior to anti-cancer therapy in the following high risk groups: highly cytotoxic chemotherapy with potential profound neutropenia based on the physician's risk assessment of the chemotherapy, and in the setting of stem cell transplantation.

Testing should be performed using RT-PCR 48-72 hours prior to the anticancer therapy. We also suggest that every cancer patient should be evaluated and assessed for risk of COVID-19 exposure and infection. Special attention should be given to older patients over the age of 65, poor performance status > 1 and multiple comorbidities. RT-PCR testing may be considered if the treating physician feels clinically indicated. Testing using serum antibody or serum antigen has no established role in cancer patients and should not be used. There is a need for prospective trials to assess this intervention, and the outcome of such intervention. Current recommendations may change based on new and emerging evidence.

Conflict of Interests: All the authors have no affiliations that might represent a conflict of interest or that might directly or indirectly influence the content of this article.

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