Peer Review File

Article information: https://dx.doi.org/10.21037/tbcr-23-10

Reviewer Comments

Comment 1: Review of English language, a few small mistakes
Reply 1: Thanks for your suggestion, we revised our language accordingly.

Comment 2: Regarding the four clinical subtypes of COVID, it is worth noting that aggravation of the clinical disease is sometimes seen around day 5 of the infection, so classification based only on initial symptoms at diagnosis may misclassify some patient's disease severity
Reply 2: In the formulation of this key point, we mainly focus on patients with mild to moderate and asymptomatic infections who account for the largest proportion of post-infection, and put forward diagnosis and treatment recommendations for breast cancer patients with different infections and cured infections in the new era of the epidemic. In the process of clinical treatment, the patient's actual situation will be grasped and evaluated, and individualized decision-making will be made.

Comment 3: What are level III and IV breast surgeries, is that the ones that require anaesthesia?
Reply 3: The classification criteria for surgery are based on its technical difficulty, complexity, and risk, and are divided into four levels:
level I~II: Surgeries with low or average technical difficulty, simple or uncomplicated surgical process, and low or moderate risk.
level III~IV: Surgeries with high technical difficulty, complex surgical process, and high risk.

Comment 4: Severe or critical COVID-19: if this means patients who require hospitalisation most guidelines recommend anticoagulation for all, which would cover the risk of thrombosis and avoid having to stop tamoxifen
Reply 4: Considering the high risk of thromboembolic events in critically ill patients, the use of tamoxifen will increase the risk of thromboembolism. If a severe infection develops in a breast cancer patient taking tamoxifen, hormone therapy should be suspended and thromboprophylaxis recommended.

Comment 5: (Neo)adjuvant therapy: there's not enough data supporting COVID-19 mortality to be lower if you delay anti-cancer treatment for more than one month (see also Geukens et al ESMO Open 2022), while you risk compromising their cancer mortality. Delays for more than 1 month should be avoided in any patient in curative setting while we await better/more relevant data (vaccinated population). The same accounts for switching from a dose dense to a 1x/3w schedule, is there any data supporting this would reduce covid mortality?
Reply 5: The section on (Neo)adjuvant therapy in the article did not mention that

delaying anti-tumor treatment for more than one month would reduce COVID-19 mortality rates. Currently, there is no data to support that the 3-week regimen can effectively reduce COVID-19 mortality rates. The purpose of recommending the 3-week regimen is to reduce the number of hospital visits and thus minimize the risk of infection for patients.

Comment 6: The authors should better look into the data available supporting the effect of chemotherapy and immunotherapy delay on covid mortality, and state this in their paper to back their decisions. Especially in the curative setting, the risk of missing a chance to prevent a relapse is higher than the risk of dying from COVID-19 which is often low in many of these generally fit patients. In the metastatic setting, prognosis is poorer (specifically in lung metastases), so delay of treatment might be more appropriate as compared to in the curative setting.

Reply 6: We highly agree with your consideration of anti-tumor therapy for patients with advanced breast cancer with COVID-19, and the consensus panel has the same consideration as you, so in this part of the article we have emphasized the importance of individualized treatment, such as mentioning that " Because patients with advanced breast cancer are always tumor-bearing, the risks and benefits of systemic treatment should be weighed when making clinical decisions during SARS-CoV-2 infection. During the COVID-19 pandemic, the timing and intensity of anti-tumor therapy should be based on the molecular type of breast cancer, tumor burden, tumor progression, and physical status of the patients.", and "For patients with high tumor burden and critical tumor conditions, the expert panel recommends that the treatment decision should be individualized after a comprehensive assessment of the tumor burden, symptoms of COVID-19, and patient's performance status and by weighing the risks and benefits of the treatments.".

There is indeed some clinical data to support the idea that chemotherapy and immunotherapy need to be delayed during coronavirus infection. Reference 28 cited in our article suggests that patients who received chemotherapy in the first seven days of COVID-19 onset had a significantly higher probability of becoming critically ill (RR=13.886, P=0.049; HR=13.909, P=0.043). References 31-32 suggest that immune checkpoint inhibitor therapy is a factor associated with hospitalization and serious adverse effects, as well as higher rates of mortality. However, there are also some different data suggesting that chemotherapy and immunotherapy do not have a significant effect on mortality (Lancet Oncol. 2020 Oct; 21(10):1309-1316.). In summary, we believe that mortality is not the gold standard for measuring whether medication is delayed, and that safety during treatment is equally important for cancer patients experiencing COVID-19 and needs to be comprehensively assessed based on the risk of disease progression. We have updated the above points in the article.

Comment 7: For myocardial enzyme testing, it is unclear if the panel recommends withholding anti-HER2 drugs until normalisation of the enzymes, and if yes, what evidence there is that this would decrease cardiac toxicity from anti-HER2 agents post covid infection.

Reply 7: After literature review, there was no study on the cardiotoxicity of anti-HER2 drugs in patients with HER2-positive breast cancer after COVID-19 infection. Because anthracyclines and anti-HER2 drugs can damage myocardial cells, and most patients with severe COVID-19 infection will have myocardial injury, so it is inferred that these drugs may increase myocardial injury in patients with COVID-19. International guidelines recommend cardiac function and cardiac biomarkers testing when using drugs in this situation. Considering the patient's medication safety, the panel recommends that after myocardial enzyme detection, combined with the patient's condition, whether to restart medication should be evaluated.

Comment 8: G-CSF: it is unclear if the panel recommends withholding the administration of G-CSF until the patient is asymptomatic from COVID infection
Reply 8: Whether G-CSF can be used for asymptomatic infection remains to be verified. A retrospective study found that G-CSF use was significantly associated with an increased risk of hospitalization in patients with COVID-19 infection (HR: 3.54; 95%CI: 1.25-10.0, P = 0.17), and the relationship between the two was also significant in patients with COVID-19 asymptomatic infection (HR: 18.31; 95% CI: 2.51-96.8, P = 008). Another prospective study found that rhG-CSF treatment of patients with new coronary infection with lymphopenia but no complications did not accelerate clinical improvement, but the proportion of patients with critical illness or death was relatively reduced. Clinicians should consider individual patients. If severe neutropenia occurs in tumor patients with new coronary infection, therapeutic use of G-CSF may help prevent secondary bacterial infections in patients. After receiving G-CSF, it is recommended to use imaging Monitor for possible pneumonia with medical measures (eg, chest x-ray).

Comment 9: CT before radiotherapy: it is unclear if the panel recommends withholding radiotherapy until pneumonia signs in the lungs have disappeared, which can sometimes take a long time
Reply 9: If the patient has imaging manifestations of pneumonia before restarting radiotherapy, it is recommended to suspend chest radiotherapy. In clinical practice, the risks and benefits of timely radiotherapy and delayed radiotherapy should be comprehensively considered, and individualized decision-making should be made. For some emergency radiotherapy and radical radiotherapy patients, restarting radiotherapy can be considered after evaluation by clinicians.