

Novel Coronavirus Infection – Knowns and Unknowns with Particular Reference to Oncology – Combating against COVID-19 with “COVID”

Abstract

We are facing yet another global pandemic with the novel coronavirus (COVID-19) outbreak and anticipate that second and even third wave of the infection may come if we do not practise constant vigilance! An advent of a mysterious outbreak of atypical pneumonia in December 2019, traced from the seafood wholesale market in Wuhan of China, spread the wings over the world in very short span. Like both severe acute respiratory syndrome coronavirus (CoV) and MERS-CoV infections, the risk of severe disease increases substantially with age and with the presence of underlying conditions. While cancer is a prevalent disease and a global health challenge, little information is available with regard to the implications of COVID-19 for cancer patients. So far, the data have been limited and fragmented. COVID-19 with different primary cancer types will have different biological behaviours with highly variable disease courses and diverse treatment strategies. Any generalized conclusions for all cancer patients with respect to COVID-19 should be interpreted with caution until we have sufficient prospective data. Enormous work needs to be done to study the specific unmet needs of cancer patients with the challenge of the COVID-19; the prevention still is the best remedy. Infection control measures should be enforced continuously, and public health education and engagement should be highly recommended. We propose to join hands together to combat against COVID-19 with some simple tips for our cancer patients to raise their awareness of this public health challenge – combating against COVID-19 with “COVID:” Continue “social distancing;” Omit unnecessary face-to-face meeting or meal gathering or mass event, make use of cyber meeting, and bring one’s own lunch box to work; Visage protection, i.e. universal precaution with surgical masks when going out in a large crowd such as public transport or any close contact in high-risk area; Infection control of the hands with hand hygiene at all times and; Diet, lifestyle, and exercise continue to be balanced and healthy.

Keywords: Cancer, COVID-19, novel coronavirus, oncology

Introduction

On March 11, 2020, the World Health Organization (WHO) characterized the novel coronavirus (COVID-19) outbreak a global pandemic.^[1] This was dated back to the advent of a mysterious outbreak of atypical pneumonia in December 2019, which was traced to a seafood wholesale market in Wuhan of China. Over the past 3 months, the COVID-19 has captured global media, political, as well as scientific attention. There have been various publications on the epidemiological and clinical features of the infection. This review article attempts to highlight the latest update of the COVID-19 infection and explore any potential implications with particular reference to cancer patients though the data have been limited and fragmented.

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Epidemiology

Four strains of coronaviruses (CoVs) are known to spread easily in humans, causing generally mildly acute respiratory illnesses known as common cold.^[2] A much larger number of CoVs have been detected in animals, particularly bats, but have not been found in humans.^[3]

On December 31, 2019, the Wuhan Municipal Health Commission announced a cluster of cases of viral pneumonia of unexplained etiology. The Southern China Seafood Wholesale Market in Wuhan was suspected to be related to the first 27 pneumonia patients without identified pathogenic agents that were reported in the late December 2019.^[4] Most of these early patients were reportedly either shop owners, largely in the West District of Southern China Seafood Wholesale Market, or people who visited the market before

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the symptom onset. This market is a large open complex of 50,000 sqm including various sections with some selling a wide variety of live wild animals for consumption. Environmental disinfection of the Southern China Seafood Wholesale Market was initiated on December 30, 2019.

The novel CoV, known as 2019-nCoV at that time, was officially identified as the cause of the disease outbreak in Wuhan on January 9, 2020. Following this official announcement of genetic sequence of the virus, 41 laboratory-confirmed cases with pneumonia were reported in Wuhan, among which the earliest known case had disease onset dated December 8, 2019.^[5] At that time, approximately 70% of these first 41 confirmed patients were reported to have exposure to the Southern China Seafood Wholesale Market.^[6]

On January 13, 2020, Thai health authorities reported an imported case in a person in his 60s who had traveled from Wuhan. This patient did not visit the Southern China Seafood Wholesale Market but reported visiting another wet market in Wuhan. On January 16, 2020, Japanese health authorities reported a confirmed imported case in a person in his 30s who had traveled from Wuhan and landed in Kanagawa on January 6, 2020. This person had not visited any wet market in Wuhan but had visited a close relative who was in hospital with pneumonia in Wuhan. Subsequently, an exported case to Seoul in South Korea was reported on January 20, 2020, with no prior history of visiting any wet markets in Wuhan or any contact with any confirmed patient. The lack of exposure history to wet markets in the generally mild exported cases indicated that there might be a larger number of undetected infections in Wuhan.^[7] On January 18, 2020, the National Health Commission taskforce was established, and while there was increasing number of new infections in Wuhan, there were travelers coming from Wuhan, diagnosed as confirmed patients in Beijing, Shenzhen, with further exported cases reported in Taiwan and the United States on January 21, 2020. Given the cases reported outside Wuhan have mostly not been severe, it was inferred that there might be a large number of undetected relatively mild infections in Wuhan.^[7] The outbreak was declared a Public Health Emergency of International Concern on January 30, 2020.^[1] The WHO further announced a name for the new CoV disease: COVID-19 on February 11, 2020.^[1]

Diagnostic Criteria and Clinical Features

While the case definition for the initial first batch of 41 laboratory-confirmed patients was not officially published, it was understood that the initial case definition required (i) fever, (ii) chest X-ray evidence of pneumonia, (iii) normal or low white cell count or low lymphocyte count, (iv) antibiotic treatment for 3 days without improvement, (v) history of recent visits to Wuhan with direct or indirect exposure to a wet market, and (vi) a respiratory specimen positive for 2019-nCoV and confirmed as 2019-nCoV by whole-genomic sequencing.^[7]

In a study of a family cluster of six patients who traveled from Wuhan from Shenzhen during December 29, 2019, and January 4, 2020, five family members were identified infected with the virus. In addition, one family member who did not travel to Wuhan became infected with the virus after several days of contact with four of the family members. None of the family members had contacts with Wuhan markets or animals, although two had visited a Wuhan hospital. Five family members (aged 36–66 years) presented with fever, upper or lower respiratory tract symptoms, or diarrhea or a combination of these 3–6 days after exposure. They presented to The University of Hong Kong - Shenzhen Hospital 6–10 days after symptom onset. They and one asymptomatic child (aged 10 years) had radiological ground-glass lung opacities. Older patients (aged >60 years) developed more systemic symptoms, extensive radiological ground-glass lung changes, lymphopenia, thrombocytopenia, increased C-reactive protein, and lactate dehydrogenase levels. The nasopharyngeal or throat swabs of these six patients were negative for known respiratory microbes by point-of-care multiplex reverse transcription-polymerase-chain reaction (RT-PCR), but five patients (four adults and the child) were RT-PCR positive for genes encoding the internal RNA-dependent RNA polymerase and surface spike protein of this novel CoV, which were confirmed by Sanger sequencing. Phylogenetic analysis of these five patients' RT-PCR amplicons and two full genomes by next-generation sequencing showed that this is a novel CoV, which is closest to the bat severe acute respiratory syndrome (SARS)-related CoV found in Chinese horseshoe bats. This supports person-to-person transmission of this novel CoV in hospital and family settings, and the reports of infected travelers in other geographical regions.^[8] Similar findings were supported by a study of 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in China through January 29, 2020. Ground-glass opacity was the most common radiological finding on chest computed tomography (CT).^[9]

Rapid Detection and Adequate Control

Rapid and accurate detection of the COVID-19 is crucial in controlling the outbreak in the community and hospitals. Nasopharyngeal and oropharyngeal swabs are recommended upper respiratory tract specimen types for COVID-19 diagnostic testing. However, the collection of these specimen types requires close contact between healthcare workers and patients, which poses a risk of transmission of the virus to the healthcare workers. Furthermore, the collection of nasopharyngeal or oropharyngeal specimen causes discomfort and may cause bleeding, especially in patients with thrombocytopenia.^[8] Thus, nasopharyngeal or oropharyngeal swabs are not desirable for serial monitoring of viral load. Sputum is a noninvasive lower respiratory tract specimen, but only 28% of patients with COVID-19 in one case series could produce sputum for diagnostic evaluation.^[10]

Saliva specimens can be provided easily by asking patients to spit into a sterile bottle. This noninvasive collection of the saliva can greatly minimize the risk of exposing any healthcare workers to the COVID-19. In Hong Kong, the COVID-19 testing was performed by Public Health Laboratory Services Branch in Hong Kong for patients who fulfilled the reporting criteria or enhanced surveillance criteria.^[11] Saliva was collected by asking the patients to cough out saliva from their throat into a sterile container, and 2 ml of viral transport medium was added. The COVID-19 virus was detected in the self-collection saliva of 91.7% (11/12) of the patients with the serial saliva viral load monitoring showing generally a decline trend.^[12] This has allowed specimen collection outside the hospitals, where airborne-infection isolation rooms are not available, and the elimination of waiting time for specimen collection, thus leading to sooner availability of the results.

COVID-19 and Cancer

Like both SARS-CoV and MERS-CoV infections, the risk of severe disease increases substantially with age and with the presence of underlying conditions.^[7,13-15] In the study of the family cluster treated in Shenzhen, the three oldest patients in the family with comorbidities had more severe systemic symptoms of generalized weakness and dry cough. As expected, they might have decreased total white blood cell, lymphocyte, or platelet counts, with also extended activated thromboplastin time and increased C-reactive protein level. Their lung involvement was also more diffuse and extensive than those of the younger patients.^[8] Higher mortality rate was also associated with baseline multiple comorbidities with the first death from the COVID-19 in Hong Kong for a 39-year-old relatively young man but known history of long-standing diabetes mellitus.^[10,16] While cancer is a prevalent disease and a global health challenge, little information is available with regard to implications of COVID-19 for cancer patients. So far, the data have been limited and fragmented.

Higher risk of complications and severe events of COVID-19

There was one relatively cancer-focused comment by Liang *et al.* in The Lancet Oncology; sharing of 1590 patients confirmed with COVID-19, 18 patients had a history of cancer. Lung cancer was the most frequent type (28%, 5/18 patients). Four (25%) of 16 patients (2/18 having unknown treatment status) with cancer and COVID-19 had received chemotherapy or surgery within the past month at the time of diagnosis, and the other 12 (75%) patients were cancer survivors in routine follow-up after primary definitive surgery. In this relatively small sample of cancer patients with COVID-19, compared with patients without any cancer, those COVID-19 patients with cancer were older (mean age 63.1 vs. 48.7 years), more likely to have a smoking history (22% 4/18 patients vs. 7% 107/1572 patients), and more severe baseline CT manifestation (94% 17/18 patients vs. 71% 1113/1572 patients). Furthermore, cancer patients

with COVID-19 were observed to have a higher risk of severe events (a composite endpoint defined as the percentage of patients being admitted to the intensive care unit requiring invasive ventilation, or death) compared with patients without cancer (39% 7/18 patients vs. 8% 124/1572 patients; Fisher's exact $P = 0.0003$).^[17] Indeed, this sample size is relatively small with much heterogeneity within the cancer population with COVID-19 in the cohort as different primary cancer types will have different biological behaviors with highly variable disease courses (0–16 years) and diverse treatment strategies. This will not be an ideal representation of the whole cancer population with COVID-19 confirmation. Thus, any conclusions that generalize to all cancer patients with respect to COVID-19 should be interpreted with caution until we have sufficient prospective data with in-depth study of this subset of population.^[18]

Greater challenge for prompt diagnosis of cancer, especially lung cancer

While the current data seemed to echo patients with underlying diseases including background of cancer would have higher risk of a protracted course of the COVID-19 and higher risk of severe events, the background radiological features of COVID-19 may also be a confounding factor making diagnosis of cancer, especially lung cancer more difficult and challenging. The diagnosis and treatment of lung cancer patients have been challenged greatly because of extraordinary public health measures since the lung cancer patients are part of the high-risk population during the COVID-19 outbreak period.^[19] Vigilant protection for lung cancer patients is needed to avoid infection. In the background of COVID-19, lung cancer patients are difficult to differentiate from the patients with COVID-19 in terms of clinical symptoms, which may bring extra challenge to the clinical diagnosis and management of lung cancer patients, with potential additional physical and psychosocial unmet needs of the lung cancer patients.

The dilemma to treat or not to treat or wait and see

While Liang *et al.* have demonstrated that cancer patients are prone to have increased risk of severe infection,^[17] many cancer patients or even their carers may prefer to delay their cancer treatment during the time of the COVID-19 epidemic in line with social distancing and to reduce the exposure to high-risk area such as clinics and hospitals. Some may opt to withhold or delay their treatment with the fear and anxiety for COVID-19 and its complications, while the risk of disease progression with no timely treatment or dose intensity of treatment being compromise in the course of anticancer treatment will make the issue more complicated and controversial. Though the current data is limited, there has been a case report published by our Chinese colleagues recently on a patient with advanced adenocarcinoma of the lung progressed after gefitinib and EGFR T790M detected with osimertinib started since September, 2017, was also diagnosed with COVID-19 confirmed with throat

swab for COVID-19 on real time reverse transcription-polymerase-chain reaction (RT-PCR) on 26th January, 2020, he was treated with cocktail therapy for his COVID-19 with cefoselis, oseltamivir, meropenem, teicoplanin and moxifloxacin while continuing his lung cancer treatment with osimertinib. Follow-up CT showed stable disease for both the lung cancer and radiological improvement for the COVID-19.^[20] Of course, this is an illustration demonstrating continuation of anti-cancer treatment in a patient with good performance status and good baseline clinical condition at the diagnosis of COVID-19, yet in the era of personalize cancer medicine and precision oncology, further prospective studies are in urgent need to see if this can be generally applied to all cancer patients with all clinical subtypes or that there are potential specific predictive, prognostic clinical factors or biomarkers to help us to make an informed personalised clinical decision for the best benefit of the patients.

Same should be applied with patient-oriented clinical strategies for treating pediatric cancer during the outbreak of COVID-19 as children with cancer are assumed to be more susceptible to COVID-19. A reasonable treatment strategy between epidemic prevention and anticancer therapy under the current epidemic conditions needs to be well planned with multidisciplinary approach. Strict implementation of prevention and protective measures for both healthcare workers and patients, the engagement of hand hygiene, medical waste management, and other hospital infection control work should be enforced.^[21]

Stepping up infection control measures to prepare for potential community outbreak and to ensure continuity of quality cancer care

While the outbreak of COVID-19 is spreading rapidly, public health experts have been advising for “social distancing” and strengthening the control of “personnel mobility.” With the limited resources of personal protective equipment and the ever-increasing demand by all healthcare workers across all countries, various healthcare organizations have been trying to postpone elective or nonurgent follow-up appointments for cancer patients, especially the cancer survivors, to space out the human flow. This has also been seen in other nononcology departments and clinics, and this may delay diagnosis of some newly presented cancer patients or missing to address to active complaints of those who have been stable, including cancer survivors.

Yet, to balance equal access to treatment and to minimize the unnecessary human-to-human transmission, and with the understanding that the COVID-19 has rapidly emerged as a global health threat which will remain as a global health challenge to all of us for a while, the initiative to step up infection control measures in individual departments or clinics, especially for those serving high-risk patients such as cancer centers, should be seriously considered. This has been started in nononcology departments such as the stepping up of infection control in ophthalmology to minimize COVID-19

infection of both healthcare workers and patients.^[22] We hope through the stepping up infection control measures for COVID-19 infection in all cancer centers could help all oncologists locally and globally to prepare for any potential community outbreak in the current fight of the global pandemic. Furthermore, all medical oncologists should work closely with all disciplines, especially the local infection control teams to implement the most optimal infection control measures appropriate for individual clinical setting through our conventional “multidisciplinary team approach” (MDT).

Relieving distress for cancer patients and their carers

Distress is the sixth vital sign for all cancer patients and their carers. While screening for distress is one way to measure psychological dimensions of cancer patients’ experiences, and doing so is increasingly part of standard operations,^[23] addressing the extra distress among cancer patients in the era of COVID-19 pandemic is of paramount importance. Indeed, since appearance of COVID-19 which has now progressed to a global pandemic, there has been flurry of scientific activity and publication surrounding this novel agent, further igniting serious cross-cutting media, as well as scientific and political debate as the more we know, the more we know how much we do not know. Reporting of the situation in real time from the public on social media could lead to more accurate collating of information by the media. Yet, the rapid pace of developments, increasing case detection rates, along with increasing diversity of information with information overload, may make the general public, especially cancer patients and their carers who understand they are of higher health risk, difficult to assimilate all these information, or difficult to make any meaningful interpretations from all the resources. The inability to validate information in a timely manner can fuel speculation and making the audience, especially the cancer patients more anxious with more media and public concern. It is recommended that the media should focus on having altruistic intentions and develop dialog with the appropriate experts and authorities to protect global health security through effective amiable partnership and collaboration.

Perhaps, on top of social distancing and the advocacy of continuous vigilance, seamless communication with compassion and care is equally important for our cancer patients, especially this time of the year with the challenge of COVID-19. While hospital or clinic visits are delayed for some of the patients due to the COVID-19, additional psychosocial support or psychological counseling through the cyberspace or telephone calls dedicated for cancer patients should be considered.^[24] This would certainly help to maintain the general well-being of our cancer patients and their carers, physically, mentally, psychosocially, and spiritually.

Combating COVID-19 with “COVID”

While much work needs to be done to study the specific unmet needs of cancer patients with the challenge of the

COVID-19, be it at the patient level or at the healthcare management level, from diagnosis to treatment and follow-up, prevention is always better than cure. Prevention of the COVID-19 is equally important as cancer prevention.

With that, vigilant infection control measures should be enforced continuously, and public health education and engagement should be highly recommended. At the time of writing of this manuscript, the WHO has just declared the COVID-19 as a global pandemic; we anticipate second and even third wave of the infection may come if we lose our vigilance. We propose to join hands together to combat against COVID-19 with some simple tips for our cancer patients raise their awareness of this public health challenge – combating against COVID-19 with “COVID:”

1. Continue “social distancing”
2. Omit unnecessary face-to-face meeting or meal gathering or mass event, make use of cyber meeting and bring one’s own lunch box to work
3. Visage protection, i.e. universal precaution with surgical masks when going out in a large crowd such as public transport or any close contact in high risk area
4. Infection control of the hands with hand hygiene at all times and
5. Diet, lifestyle, and exercise continue to be balanced and healthy.

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Conflicts of interest

There are no conflicts of interest.

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