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Highlights of the issue

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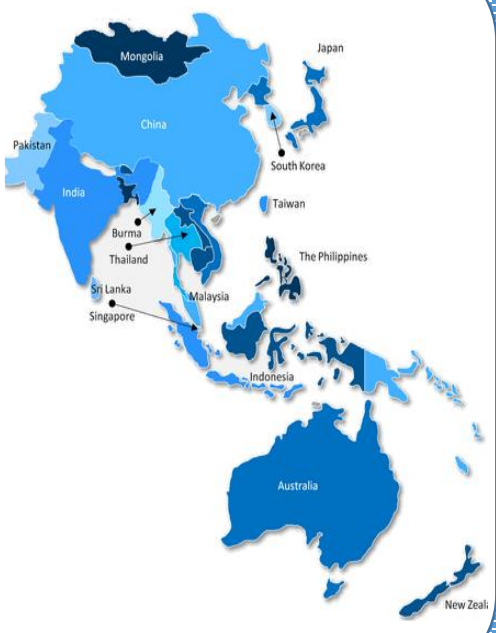
- An Asian Perspective of the Management of COVID-19: the Asian National Cancer Centers Alliance.. By Mela Dewi et. al.



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EDITORIAL

Healthcare Systems Need to be Organized to Fight two Pandemics Simultaneously

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Corona Virus Disease (COVID-19) dashboard shows that the pandemic caused by SARS-CoV-2 of the World Health Organization (WHO) virus has claimed about 450,000 lives across the globe within six months since the first reported outbreak in December 2019 [1]. The COVID-19 outbreak has strained the health systems to the extreme and will deeply impact their capacity to tackle the other ongoing pandemic, caused by the growing burden of cancer.

A pandemic is defined as "an epidemic occurring worldwide, crossing international boundaries and usually affecting a large number of people" [2]. Going by that definition, the world has been grappling with cancer pandemic much before COVID-19 struck. Cancer, causing nearly 10 million deaths every year, ranks as the number one cause of premature mortality in 48 countries, second in 43 countries and third or fourth in another 22 countries of the world [3]. In rest of the 58 countries the disease ranks among five to ten leading causes of premature deaths.

SARS-CoV-2 infection creates a huge burden on the health infrastructure as it spreads very fast and has high infection-fatality ratio (IFR), 5-10 times that of seasonal influenzas [4]. European data shows that nearly one fifth of the COVID-19 patients require hospitalization, 9% of those hospitalized require intensive care management and the case fatality is extremely high above the age of 60 years [5]. The health infrastructure is further crippled by the fact that 20% of all people infected are frontline health providers. A weakened health system with priorities shifting back to infectious disease control will have a long term impact on the management of the patients with suspected or diagnosed cancer and also on the cancer prevention interventions delivered through public health programmes.

Two recently published studies in the Lancet clearly show that treating cancer patients during the epidemic does not increase COVD-19 related mortality. The authors strongly argue that withholding treatment would cause significantly more harm than COVID-19 itself, for the cancer patients. The COVID-19 and Cancer Consortium published data on 928 adults with active or past cancer (median age 66 years, 39% on active anticancer treatment) who had confirmed coronavirus infection [6]. All-cause mortality among these patients recruited in Spain, Canada and the USA was 13% within 30 days of diagnosis of infection. The risk of mortality increased with increased age, male sex, former smokers, associated comorbidities, active cancer and poor performance score. The reassuring finding was that recent anticancer treatment including surgery did not increase mortality. The UK Coronavirus Cancer Monitoring Project reported that 28% of 800 cancer patients with Coronavirus infection died; 93% of the deaths were due to COVID-19 [7]. Risk of death was significantly associated with the factors identified by the study mentioned earlier, but not with administration of immunotherapy, chemotherapy, radiation therapy or targeted therapy within 4 weeks of detection of SARS-CoV-2.

Cancer itself is a major co-morbidity that increases risk of death due to COVID-19, but harm-benefit ratio clearly tilts in favour of offering stage-appropriate treatment for the cancer patients without any delay. The oncology centers will continue to face major challenges due to the restrictions imposed on out-patient consultations and in-patient admissions to implement social distancing. There will be shortage of staff as some of them get infected and/or exposed and are forced to be in quarantine and disruption of supply chains for essential chemotherapeutic drugs. Organizations like European Society of Medical Oncology have published guidelines on how to continue patient care in spite of the pandemic [8]. Educating the patients as well as the staff on personal protection, maintaining social distancing as much as possible even during clinical interactions, adequate amount of protective equipment for staff as well as patients, and regular testing of patients undergoing treatment to identify, triage and treat the COVID-19 patients early are some of the key recommendations. Each oncology center should develop

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its standard operating practice in consultation with such international and national guidelines. Teleconsultation to monitor patients on oral medications or for follow up should be promoted.

The COVID-19 pandemic should not be allowed to overshadow the cancer control activities. It is difficult to predict the duration of the pandemic. Hence, some of the cancer control measures that have been temporarily put on hold as 'non-essential' should be restarted in a pragmatic manner. Many countries have halted hepatitis B and Human Papillomavirus vaccination programmes due to multiple reasons – overstretched health systems, disruptions in vaccine supply, parent's disinclination to bring children to the health facilities, closure of schools etc [9]. WHO has strongly recommended to resume vaccination activities. The interval between two doses of the HPV vaccine may be extended to at least 12 months to gain some time for the health system to recover. The impact of teleworking and working from home on obesity and reduced physical activity needs to be counteracted with active promotion of healthy practices like avoiding junk food, limited consumption of alcohol and pursuing 150 minutes of exercise of moderate intensity or 75 minutes of exercise of vigorous intensity per week. A systematic review of literature shows that the smokers have 1.4 times higher risk to have severe symptoms of COVID-19, are 2.4 times more likely to require intensive care including mechanical ventilation and 2.4 time more likely to die compared to non-smokers [10]. Educational messages should highlight this as a compelling reason to quit smoking or not to initiate the habit.

Most countries have temporarily withheld cancer screening activities. To adapt to the 'new normal' situation the programmes need to consider changes in screening and diagnostic algorithms to minimize number of visits and client-provider contacts. Switching to HPV self-sampling based screening for cervical cancer, combining diagnosis and treatment in a single visit for the screen positive women are some of the examples. Further research is needed to identify and evaluate an affordable self-testing kit for colorectal cancer screening. Men and women with co-morbidities (diabetes, hypertension, and respiratory illnesses) should have priority access to services to reduce waiting time. Use of protective equipment and frequent hand washing both by clients and providers and liberal use of sanitizers will protect both the individuals attending screening and providers.

Fear of contacting the SARS-CoV-2 infection may dissuade patients with symptoms to seek early medical consultation and lead to delayed cancer diagnosis. The health facilities should continue to practice proper infection control measures and create safe environment for all patients. The pros and cons of tele-consultation for patients with symptoms should be properly assessed. Primary health care providers with their knowledge of local conditions and their close ties with the community are well positioned to respond to the specific health needs of the population and promote cancer prevention and early detection in their community as social activities gradually resume.

The pandemic will have a huge economic impact that will push many people below poverty line and make them victims of growing inequity in accessing both preventive and therapeutic care. The health system needs to be responsive to the specific needs of the population and look beyond controlling the pandemic. The COVID-19 response strategies for the country should incorporate measures to bring back to normal the temporarily derailed NCD control measures and continue planning for the future. Else, the world will face a twin tragedy of large number of premature deaths occurring both from communicable and non-communicable diseases.

Disclaimer

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EDITORIAL

View Points in Oncology: Guiding Cancer Care in Coronavirus Disease Pandemic

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Coronavirus outbreak has adversely affected the cancer care delivery system apart from affecting the overall health system worldwide. Cancer patients are more susceptible to acquire coronavirus infection and are at an increased risk to develop severe or critical form of COVID-19 [1]. Oncology communities are having a tough time deciding treatment modifications in cancer management in view of paucity of data on different aspects of cancer care. We have evolved from December 2019 till date with many scientific guidelines regarding management of cancer patients in a background of coronavirus outbreak. Different Institutions, Hospitals, Oncology societies have put in their efforts together to formulate guidelines to ensure cancer care delivery at cancer centres.

Practice of oncology is facing many hindrances as lockdown has made it difficult for patients to present to hospitals. Almost all guidelines have advocated to continue cancer treatment with an instruction to avoid unnecessary visits to hospitals to minimise the risk of infection [2]. Oncology is an emerging speciality where facts are changing very rapidly. Cancer, from being a deadly disease, has noted a significant increase in survival for many cancer types and that became a possibility with extensive research for all tumour types.

COVID-19 has affected cancer care delivery and cancer research. Oncology communities have moved from evidence based practices to consensus guidelines. Earlier, new practices were adopted on the basis of results of randomised controlled trials with adequate sample size, but this unprecedented situation has changed our oncology perspective. We need more time to understand the harms and benefits of new practices adopted in our day to day life. Published data on practice modification from different parts of the world is the biggest learning resource to boost our confidence.

Viewpoints have never been considered as a good level of evidence and are the topics we hear being debated in point-counter-points at meetings, are also the subjects of grand rounds presentations, and are the basis of decisions that sometimes give us sleepless night. It is often considered when the controversies in oncology and oncologic science need to be defined, discussed, and debated. As we are fighting a new battle every day with new battle fronts in cancer care delivery, several types of opinion pieces, including Editorials, Commentaries, Viewpoints, Correspondence, Short Communication and Special Report, have gained importance. Each of them is serving a separate purpose to make oncology communities informed for effective cancer care in this crisis.

Viewpoints are strong point of views that provokes the community to think and make a strong stand and question his or her own stand on current issues. In COVID times, viewpoints are helping to set an agenda for cancer care.

To understand the distribution of published manuscripts on management of different cancer types, a systematic literature search was performed using PubMed database using word Cancer, COVID-19 and coronavirus disease on 23rd June, 2020. Out of 734 articles reflected on search, 267 articles were found to be associated with cancer care amidst the current pandemic. All the articles were further analyzed to see the distribution of article types and country of publication to understand the contribution of worst affected countries to guide the rest of the world. We did not consider accepted articles in pre-proof for analysis.

In our analysis, only 14% articles were found to be original articles and were mostly from USA, China and Italy (Table 1). This reflects that 86% articles were either review, guidelines or recommendations, editorial, correspondence, comment, viewpoints, communications, case report and series, that guided our fight against COVID-19. This pandemic has united us to work together and collaborate irrespective of difference in our sociocultural parameters. More than 5% published data had authors from different nations, showing oncologists have started working across the geography to minimize the challenges and boost the learning from other experience. Out of 19 articles published from India, 2 articles were found to be original study. Maximum number of articles

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Table 1. Publication statistics on Cancer Care and COVID-19 (PubMed Indexed)

Publication summary as per type of manuscripts		
Type of Manuscripts	Total Number (267)	Percent (%)
Correspondence/Letter to Editor/Comment/Commentary/View Point/ Short Communication/Special Report	111	41.57
Review	53	19.85
Recommendations/Guidelines	35	13.10
Editorial	19	7.11
Case Reports	11	4.11
Case Series	02	0.74
Original Research	36	13.48
Publication summary as per Country of Origin		
Country of Publication	Total Number (267)	Percent (%)
USA	70	26.21
China	55	20.59
Italy	46	17.22
India	19	7.11
United Kingdom	12	4.49
France	11	4.11
Germany	08	2.99
Spain	06	2.24
Brazil, Canada and Switzerland	04 each country	1.49
UAE, Hong Kong and Lebanon	03 each country	1.12
Singapore, Netherland, Hungary and Turkey	02 each country	0.74
Prague, New Zealand, Belgium, Kuwait, Japan, Peru, Morocco, Sudan, Saudi Arabia, Iran and Philippines	01 each country	0.37

have been contributed by Tata Memorial Hospital, Mumbai. Personal experiences and change in practices at institution level was the only learning resource in this crisis. List of publications in reference to article types and publishing Institutions have been summarised in Table 2. Many centres have started original studies related to problems they have encountered during this pandemic and outcome of these studies, will certainly help us to modify our cancer care practices in the best interest of our patients. It will be an important task to critically analyse the new problems associated with this crisis to optimise our cancer care facilities. Although this pandemic has made a major disruption in every aspects of cancer care, it does not necessarily mean that cancer care should come to a standstill. Oncologists are trying to overcome many challenges with personalized decision making and by implementing appropriate technological solutions.

This pandemic will probably end in coming times but learnings from this pandemic will certainly help us to formulate future interventions. This pandemic taught us to work in close collaborations, to learn from each other and to help each other to make our science and research useful to combat this crisis. This positive change will certainly help us to focus on more innovative methods to reach out to people like we did in this crisis i.e. patient consultation without meeting them face to face, knowledge update through webinars, patient educations through podcast. Viewpoints have helped us to make effective treatment decisions in view of limited evidence based data and motivated us to share our learning to rest of the world, to make our view points as a source of learning and important reference for cancer care.

Table 2. Indian Publications on Cancer Care and COVID-19 as per Institution Affiliation (Source: PubMed till 23th June 2020)

Institute Name	Journal Name	Article Type	Reference/ pdf Link
Tata Memorial Hospital, Mumbai	Head Neck	Comparative Study	[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7264597/pdf/HED-42-1173.pdf
	Head Neck	Review	[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7267519/pdf/HED-42-1144.pdf
	Indian Journal of Cancer	Special Article	[5] http://www.indianjcancer.com/temp/Indian Journal of Cancer 572123-4941821_134338.pdf
	Journal of Laparoendoscopic & Advanced Surgical Techniques	Case Reports	[6] https://www.liebertpub.com/doi/pdf/10.1089/lap.2020.0241
	Indian Journal of Surgical Oncology	Review	[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7212248/pdf/13193_2020_Article_1086.pdf
	New England Journal of Medicine	Correspondence	[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7207224/pdf/NEJMc2011595.pdf
Lady Hardinge Medical College & SSK Hospital, Delhi	Asian Pacific Journal of Cancer Prevention	Editorial	[1] http://journal.waocp.org/article_89005_932b137a411c9b5e8acfedda9acc5d5c.pdf
	Asian Pacific Journal of Cancer Prevention	Editorial	[9] http://journal.waocp.org/article_89091_04d2c6b8ac96fe06ee79f6fe78b3a9dd.pdf
	Lung Cancer Management	Commentary	[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202360/pdf/lmt-2020-0012.pdf
All India Institute of Medical Sciences, Delhi	Indian Journal of Cancer	Letter to Editor	[10] http://www.indianjcancer.com/temp/Indian Journal of Cancer572218-5014929_135549.pdf
	Indian Journal of Surgical Oncology	Case Reports	[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7201913/pdf/13193_2020_Article_1082.pdf
Post Graduate Institute of Medical Education and Research, Chandigarh	Medical Hypotheses	Hypotheses	[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7282763/pdf/main.pdf
Cancer Institute (WIA), Adyar, Chennai	Indian Journal of Surgical Oncology	Editorial	[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7188486/pdf/13193_2020_Article_1080.pdf
All India Institute of Medical Sciences, Rishikesh	Indian Journal of Cancer	Recommendations	[14] http://www.indianjcancer.com/temp/Indian Journal of Cancer 572129-4922227_134022.pdf
Tata Memorial Center, Kolkata	Journal of Global oncology	Observational Study	[15] https://pubmed.ncbi.nlm.nih.gov/32552110/
Mahamana Pandit Madan Mohan Malviya Cancer Centre, Varanasi	Indian Journal of Cancer	Perspective	[16] http://www.indianjcancer.com/temp/IndianJournal of Cancer 572221-4962881_134708.pdf
Max Healthcare, Delhi	ecancermedical Journal	Editorials	[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7289605/pdf/can-14-ed101.pdf
Manipal College of Dental Sciences, Mangalore, Karnataka	Oral Oncology	Letter to Editor	[18)] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151408/pdf/main.pdf
Kalka dental College & Hospital, Meerut, UP	Oral Oncology	Editorial	[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211608/pdf/main.pdf

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RESEARCH ARTICLE

Guidance for Facing Dilemmas of Hematopoietic Stem Cell Transplant Clinicians in the Coronavirus Disease 2019 (COVID-19) Pandemic: An Iranian Consensus

Seied Asadollah Mousavi, Sorosh Rad, Tahereh Rostami, Mohammad Vaezi, Hosein Kamranzadeh, Davood Babakhani, Sahar Tavakoli, Maryam Barkhordar, Tanaz Bahri, Amirabbas Hedayatias, Azadeh Kiumarsi

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Abstract

Background: COVID-19 has been declared as a public health emergency and a pandemic by World Health Organization. Among high-risk patients infected by the virus, hematopoietic stem cell transplant (HSCT) recipients are vulnerable to severe presentation of this infection. Thus, the necessity for precise strategies in dealing with HSCT recipients in this pandemic seems inevitable. **Methods:** We discussed the dilemmas brought up by the emergence of COVID-19 in the management of HSCT recipients, through a virtual panel of experts, considering the latest available records about COVID-19. About each enquiry, we have provided the consensus of the clinicians and paraclinicians in our center. **Recommendations:** We agreed to choose more precautious strategies and less optimal policies. The amendments aim to reduce the risk of exposure to COVID-19 in our patients and also in our health care provider team.

Keywords: COVID-19- pandemic- hematopoietic stem cell transplant

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Introduction

Coronavirus Disease 2019 (COVID-19) has been classified as a pandemic by World Health Organization since March 2020 [1]. The number of involved cases is increasing rapidly around the world and its burden on health care system is progressively growing. Most countries have restricted their gatherings, travels, and other aspects of life. These restrictions would surely impact the transplant activities in many centers. Although all people are susceptible to this infection, hematopoietic stem cell transplant (HSCT) recipients are at increased risk and dissimilar to other respiratory viruses, little is known about the clinical significance of human coronavirus infection in this population.

Therefore, in this paper, we have provided the recommendations from hematology-oncology and stem cell transplant research center (HORCSCT) experts on managing HSCT recipients and donors in COVID-19 pandemic. It is imperative to note that data about this disease and its impact on our patients is evolving and so our strategy is to repeatedly update the guidance as soon as new information becomes accessible.

Epidemiology and clinical features

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARSCoV-2), which is a novel single-stranded enveloped RNA virus. Respiratory droplets are the most important route of transmission but it can also be aerosolized or detected in the stool. As noted by Food and Drug Administration (FDA), transfusion-transmitted coronaviruses has not been reported till now [2]. The virus incubation time is estimated to be 2-14 days [3]. Early reports suggest that the majority of patients have mild symptoms with the most common being fever and dry cough [4]. Moreover, symptoms related to the digestive

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systems, such as nausea and diarrhea, and ophthalmic symptoms are also part of the clinical manifestations [5]. Nevertheless, the asymptomatic patients are important sources of transmission during the incubation period or in early stages of infection [6]. Imaging manifestations include multiple small patchy shadows and interstitial changes at an early stage, which gradually progresses to multiple ground-glass and infiltration opacities in both lungs during the progressive stage [7]. Patients with COVID-19 are prone to have a decrease in lymphocyte counts, and levels of inflammatory markers, such as C-reactive protein (CRP), may be elevated in some patients to a varying degree [8]. Mortality seems to be age dependent, with the highest proportions in older patients. Even though co-morbidities have been reported in most case series, documented data about transplant patients is limited and a sketch of the disease in HSCT recipients is not yet available. The main diagnostic test is RT-PCR of nasopharyngeal, oropharyngeal and lower respiratory tract samples. It should be noted that following infection, median viral shedding of 20 days is anticipated which might be more prolonged in immunosuppressed patients and may last up to 4 weeks [9]. For treatment, antiviral drugs such as lopinavir-ritonavir and remdesivir and anti-cytokine therapies such as tocilizumab are under exploration in different clinical trials [10].

Methods

The existing guidelines about the management of HSCT patients in COVID-19 pandemic were discussed among HORCSCT experts through a virtual panel [11]. Considering the available updates on COVID-19, we debated on the proposed dilemmas and the frequently asked questions by patients and health care professionals and then we documented the consensus of all members in the related disciplines.

Recommendations

Based on the experiences with other infectious disease, the available health care facilities in our country, and the existing data in the literature, these recommendations are proposed for the time being and they would be updated as soon as new information about COVID-19 epidemiology and clinical outcomes would become accessible.

In HSCT candidates

• In patients not known to have COVID-19 (asymptomatic (The significant considered symptoms are fever, cough, shortness of breath) AND no history of close contact with a diagnosed case of COVID-19)

- Recommend patients for home isolation 14 days before hospital admission.

- Check for CBC, Diff, CRP and COVID-19 test by RT-PCR before admission.

- A negative result of COVID-19 test (by RT-PCR), 48 hours before the initiation of conditioning regimen is demanded.

• Patients known or suspected to have COVID-19 (symptomatic OR history of close contact with a diagnosed case of COVID-19)

- Check for CBC, Diff, CRP, COVID-19 test by RT-PCR and chest CT scan before admission.

- For patients with a positive RT-PCR test for COVID-19 or chest CT scan suspicious of COVID-19, who are considered high risk for disease progression (i.e. acute leukemia, high-grade lymphomas), HSCT should be deferred until symptoms are resolved AND two separate negative RT-PCR tests, at least 1 week apart, are obtained.

- For patients with a positive RT-PCR test for COVID-19 whose underlying disease is considered low risk, HSCT should be deferred for at least 3 months.

- In patients who have a history of close contact with a known case of COVID-19, but their RT-PCR test for COVID-19 is negative and their chest CT scan is normal, conditioning regimen should be deferred until 14 days after the mentioned contact AND one negative RT-PCR test should be obtained before the initiation of conditioning regimen.

• Defer following autologous HSCTs until the risks associated with the COVID 19 pandemic have passed: non-urgent indications (i.e. Multiple Myeloma in first complete remission (As some novel agents like Ibrutinib or Daratumumab aren't easily available for multiple myeloma patients, we can only defer auto-HSCT for patients in their first complete remission), low-grade lymphoproliferative diseases, and consolidative transplants for solid tumors such as germ cell tumors) and non-malignant indications

• Defer following allogeneic HSCTs until the risks associated with the COVID 19 pandemic have passed: HSCTs from international unrelated donor and HSCTs for non-malignant disorders (i.e. Thalassemia, etc.)

In stem cell donors

Few is known about the risk of COVID-19 transmission from donor to recipient. Attention to donor epidemiological risk factors may help to weaken the risk of donor transmitted infection [12].

• In donors not known to have COVID-19 (asymptomatic AND no history of close contact with a diagnosed case of COVID-19)

- Recommend donors to sustain good hygiene and avoid crowded residences for at least 28 days before donation.

- Test for COVID-19 by RT-PCR one day before the initiation of conditioning regimen.

• In donors suspected to have COVID-19 (symptomatic OR history of close contact with a diagnosed case of COVID-19)

- Check for COVID-19 test by RT-PCR and chest CT scan.

- In donors with a history of close contact with a diagnosed case of COVID-19, if the RT-PCR test for COVID-19 is negative AND the chest CT scan is normal, the donor would be considered eligible for donation if 14 days has passed from the mentioned last contact AND one negative RT-PCR test obtained before starting conditioning regimen.

- If the RT-PCR test for COVID-19 is positive OR the chest CT scan is suspicious of COVID-19, the donor would

be considered ineligible to donate for at least 3 months after the complete resolution of symptoms.

- If HSCT is urgent and there are no alternative suitable donors available, re-consider the donor's eligibility; if at least 28 days has passed from complete resolution of symptoms AND there is no history of severe respiratory disease AND one negative RT-PCR test could be obtained before starting conditioning regimen, the donor would be considered eligible for donation.

• As harvesting stem cells from bone marrow requires anaesthesia and referring the donor to the general operation room, in which the donor may be exposed to COVID-19, we prefer to choose peripheral blood as the source of stem cells, for the time being.

Recommendations for HSCT recipient's caregiver

• The patient should not have a caregiver if possible.

• The caregiver's COVID-19 RT-PCR test should be negative before entering HSCT ward.

• Caregivers with COVID-19 symptoms are ineligible and should be referred to national guideline for diagnosis and management of COVID-19.

• Caregivers who have a history of close contact with a diagnosed COVID-19 case, should avoid contacting the patient for at least 14 days after the mentioned contact and obtain a negative COVID-19 RT-PCR test before entering the HSCT unit.

Recommendations for HSCT unit

• SARS-CoV-2 is sensitive to ultraviolet rays and heat. The virus can be effectively inactivated under conditions of 56 °C for 30 min, using ether, 75% alcohol, chlorine-containing disinfectant, and chloroform [13]. Disinfection of HSCT wards should be performed with alcohol containing disinfectants.

• People's commute in HSCT unit should be restricted as much as possible and non-essential staff & student contact with inpatients should be reduced.

• Face-to-face educational assemblies should be postponed and education should be provided via teleconferencing or other electronic layouts [14].

• The HSCT unit's workforce including administrators, ward staff, and clinicians should be re-educated about hand hygiene practices, policies for respiratory virus isolation and the major associated symptoms of COVID-19.

• RT-PCR for COVID-19 is planned to be offered as a screening tool, every two weeks in HSCT units' working staff.

• If employees of HSCT units are symptomatic or have a history of close contact with a diagnosed case of COVID-19, they should leave the unit immediately and should be referred to national guideline of diagnosis and management of COVID-19.

Recommendations for recipients in post-transplant phase:

• Patients after being discharged from transplant unit should limit their contacts with potentially infected people.

• Patients should adhere to national prevention guidelines recommendations such as hand hygiene, home isolation and social distancing.

• Patients may use cyber network or telephone contact with healthcare providers to manage their non-emergent problems in order to reduce the frequency of travels to the hospital.

• Prophylaxis after HSCT with hydroxychloroquine sulfate 400 mg as single dose (Pediatric dose: 6.5 mg/kg, not to exceed 400 mg) every 3 weeks since engraftment until the COVID-19 pandemic has lapsed, is recommended.

Diagnosis and treatment of COVID-19 in HSCT patients

• For patients with upper or lower respiratory symptoms and for patients who have a history of close contact with a person diagnosed with COVID-19, RT-PCR test for COVID-19 and chest CT scan should be considered.

• Routine bronchoalveolar lavage (BAL) is not recommended if patient has a positive RT-PCR test for COVID-19 unless a co-infection is suspected.

• If RT-PCR test for COVID-19 is positive or chest CT scan is suspicious of COVID-19, patient should be managed and treated according to national COVID-19 guideline.

• Optimal management strategies have not been determined. Supportive care is the mainstay of therapy.

• For prophylaxy and treatment of graft versus host disease, immunosuppressive therapy should be continued. Drug–drug interactions of anti-viral drugs with calcineurin inhibitors should be kept in mind.

Finally, the emergence of COVID-19 is a global crisis that the transplant community has been forced to face. We should learn from our experiences and implement the best possible strategies in order to protect our transplant recipients and also the healthcare providers.

Disclosure

The authors have no conflicts of interest in this manuscript.

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RESEARCH ARTICLE

Advanced Lung Cancer Survival in Times of Economic Hardship: A Greek Paradigm

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Abstract

Objective: Greece has been affected more than any other European country from the financial crisis that began in 2010. Just 20 months after Greece exited an eight-year long aid program, forecasts of a new recession within 2020 due to COVID-19 pandemic make concerns regarding the compromise of health care quality within the new crisis relevant once again. In this study we sought to evaluate clinical outcomes in patients with advanced lung cancer in the pre-crisis and crisis era in a dedicated oncology centre in Greece. **Methods:** A retrospective analysis of 522 consecutive medical records of lung cancer patients admitted in a Greek dedicated cancer hospital between the years 2008-2013 was performed. Progression Free Survival (PFS) and Overall Survival (OS) were calculated for advanced lung cancer compared over two consecutive time periods using 2010 as a cutoff point. **Result:** 71 and 78 patients comprised the study sample for the two periods. PFS and OS were similar over the two periods (7.73 [6.42-9.04] vs. 6.03 [5.02-7.04] and 13.70 [9.61-17.79] vs. 11.08 [7.74-15.92] months, respectively). Higher Performance Status (PS) was associated with worse survival measures over both periods, while no statistical significance was reached for OS in the latter period. Dissimilarities in PFS were observed between beneficiaries of different insurance trusts. **Conclusion:** Clinical outcomes for advanced lung cancer have not changed as a result of the financial crisis in our institution. The insurance provider seems to affect health outcomes. This old paradigm could serve as new guidance in the forthcoming recession due to COVID-19 pandemic.

Keywords: Financial crisis-mortality- lung cancer- health impact- Greece

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Introduction

The relation between socioeconomic determinants and health has long been a scientific consideration and has been studied thoroughly especially during times of economic hardship [1-4].

The ongoing Covid-19 pandemic led to unprecedented mitigation interventions in many countries with profound

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sequelae on their economy thus an imminent new global financial crisis will be followed by the resurgence of discussions about economic recession effects on health [5]. As Greece had been greatly exposed to the effects of the previous global financial crisis of 2008, its recent example can provide vital information regarding effective health policy making [6].

In 2010, in the face of default, Greece was forced to sign the first - of others to follow - memorandum of understanding with the European regulating mechanisms (so called Troika), in return of bailout packages and reforms, including cuts to public health expenditure [2-4, 7].

Although the effects of austerity measures on Greece's public health have been thoroughly analyzed by the scientific community [2-4, 7], data from other health sectors, such as cancer care, remain scarce [8-9].

"Metaxa" Cancer Hospital is located at Piraeus region in Attica, Greece. With 500 beds it is probably the largest of the four dedicated cancer hospitals in the country. It serves a population of more than 2,000,000 people, but also accepts referrals from all over Greece. Treatment and hospitalization expenses in Greece are fully covered by the patients' social health insurance provider which differs according to their profession. As far as our dedicated oncology center is concerned, numerous complaints by patients regarding the compromise of their healthcare appeared on the media, during the recent economic crisis [10]. They mostly reported delays and unavailability of treatment, shortages of medication and barriers to their access to the hospital. Malfunctioning medical equipment and hospital understaffing may have also contributed to the deterioration of the quality of the provided service [11].

Driven by these allegations, we sought to investigate if clinical outcomes had changed in our patients as a result of the crisis. Using 2010 as a cutoff point, we performed a retrospective, observational single center study to examine the health outcomes for patients with advanced wild type (wt) Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) over two consecutive time periods in relation to disease specific treatment.

Lung cancer is the most common cancer in the world today and a major cause of cancer mortality. Based on histopathology, lung cancer is classified in two major categories: SCLC and NSCLC. NSCLC is further comprised mainly by adenocarcinoma (AC), squamous cell carcinoma (SCC) and large cell (LC) carcinoma. Time trends regarding the histological types have been reported, probably reflecting population – level changes to smoking behavior. Although tobacco smoking is related to all histological types, it is more strongly associated to SCC, followed by SCLC and AC. The prognosis of lung cancer remains poor [12]. Molecular abnormalities in NSCLC such as activating epidermal growth factor receptor (EGFR) mutations, are found in approximately 10 to 15% of patients with lung adenocarcinoma, resulting in changes in patient management since the introduction of targeted therapies (TKI inhibitors etc.) [13]. Chemotherapy has remained the treatment of choice for advanced lung cancer patients without detectable genetic mutations [14], thus making this category of patients suitable for comparison, over two different time periods for which there were no advances or changes in treatment.

Materials and Methods

This is a retrospective, observational single center study. The research protocol was approved by the hospital's scientific, ethics and administrative committees and statements of confidentiality were signed thus conforming to all ethical issues.

All the medical records of lung cancer patients admitted in the years 2008-2013 were examined and 2010 was used as the cutoff point in order to divide the patients in the pre-crisis (2008-2010) and crisis (2010-2013) groups. For the purpose of the study, we enrolled only clinically staged IV wt NSCLC and SCLC patients according to the American Joint Committee for Cancer- International Association's for the Study of Lung Cancer (AJCC-IASLC) 7th edition of cancer staging manual [15]. Patients had to be initially staged (not restaged) and to have been subjected to standard first line chemotherapy excluding targeted agents within 2008-2013.

The exclusion criteria comprised of inconclusive diagnosis or initial staging, unexpected (for any reason) or early discontinuation of chemotherapy resulting in unacceptable delays and incomplete regimens, missing or impossible to interpret medical record data and concurrent malignancy of such biological behavior and extend, able to affect prognosis of lung cancer or stage I-III disease.

Demographic and epidemiological data as well as survival measures, namely progress free survival (PFS) and overall survival (OS) were calculated and compared, over the two consecutive time periods. PFS was defined as time in months from first line treatment initiation to the date of radiographically or clinically observed disease progression. Similarily OS was defined as time in months from the date of diagnosis to the date of patient death.

Qualitative data - presented as absolute and value percent- were assessed by Chi-square test. Qualitative data presented either as median value (IQR) or mean value (±SD) were assessed either by non-parametric tests or student's t-test, respectively. Differences in PFS and OS -presented as median value (95% CI) - between the groups were compared by survival model (Kaplan-Meir, Log Rank Test). Statistical significance was set as two sided p=.05. Statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows).

Results

Out of 522 lung cancer admissions in the observation period (2008 – 2013), only 149 patients were eligible for inclusion in our study (stage IV wt NSCLC and SCLC, receiving standard first line chemotherapy). The alleged ''pre crisis'' and ''crisis'' periods were comprised of 78 and 71 patients respectively.

The male to female ratio was 3.47. The mean age at diagnosis was 64.27±9.60 years. Their baseline

Table 1. Patients' baseline Characteristics According to Enrollment Period

	<2010 n=71	>2010 n= 78	P
Gender, Male /Female, n	51/20	59/19	0.6
Age at diagnosis, yrs	61.8±10.53	63.73±8.73	0.22
Histology, n (%)			
SCLC	25 (35.2)	17 (21.8)	0.07
NSCLC	46 (64.8)	61 (78.2)	
Performance status, n (%)			
0	24 (54.5)	32 (54.2)	
1	14 (31.8)	20 (33.9)	0.76
2	5 (11.4)	4 (6.8)	
3	1 (2.3)	3 (5.1)	
Insurance provider, n (%)			
OGA	5 (7.1)	6 (8.1)	
IKA	45 (64.3)	38 (51.4)	
ON	4 (5.7)	13 (17.6)	0.25
OAEE	5 (7.1)	5 (6.8)	
Other	11 (15.7)	12 (16.2)	

Table 2. Progression Free Survival, Months (median [95%CI]), According to Enrollment Period

	<2010	>2010
Overall	7.73 [6.42-9.04]	6.03 [5.02-7.04]
Gender	P=0.49	P=0.22
Male	7.93 [6.36-9.49]	4.97 [3.75-6.19]
Female	7.20 [9.26-10.14]	9.03 [5.19-12.87]
Performance status	p<0.0001	p<0.015
0	9.07 [7.10-11.04]	6.50 [5.08-7.93]
1	7.33 [2.01-12.65]	4.30 [1.52-7.08]
2	7.17 [0.00-14.56]	5.33 [0.00-11.18]
3	2.03 [2.03-2.03]	2.77 [1.81-3.73]
Age at diagnosis	P=0.39	P=0.46
<65	7.00 [5.17-8.83]	4.57 [1.92-7.23]
≥65	9.07 [6.43-11.71]	6.23 [4.36-8.10]
Histology	P=0.071	P=0.942
NSCLC	8.70 [7.21-10.19]	5.60 [3.56-7.64]
SCLC	6.33 [4.53-8.13]	7.33 [4.74-9.93]
Insurance provider	P=0.061	P=0.01
OGA	12.13 [9.64-13.62]	11.07 [4.91-17.23]
IKA	7.73 [6.11-9.35]	6.47 [4.76-8.18]
ON	6.33 [4.14-8.53]	2.50 [2.17-2.8]
OAEE	8.70 [7.91-9.50]	4.37 [0.00-8.88]
Other	5.33 [1.30-9.37]	5.33 [3.00-7.65]

characteristics are shown in Table 1 according to the enrollment period (2008-2010 and after 2010). While there was no difference regarding gender, age at diagnosis, PS and insurance provider distribution between the two studied periods, there were more NSCLC subjects after 2010 as compared to those with SCLC (61 or 78.2% vs. 46 or 64.8%; p=0.07).

PFS was available for all (n=71 before 2010; n=78 after 2010) patients. The median PFS was 7.73 [6.42-9.04] and 6.03 [5.02-7.04] months (p=0.75) for the two studied periods, respectively (Table 2, Figure 1A). Gender, age at diagnosis (<65 vs. ≥65 years) and histology (SCLC vs. NSCLC) had no effect on PFS in both periods. On the contrary and as expected the higher the PS the shorter the

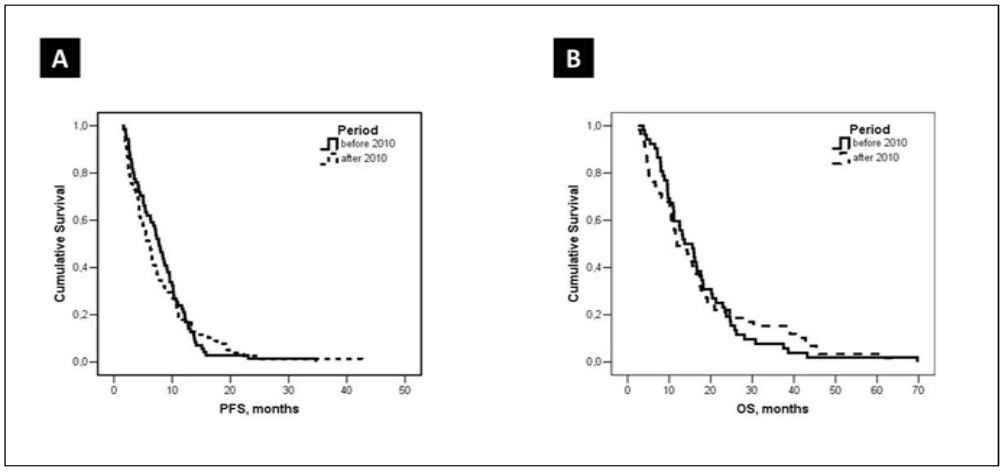

Figure 1. (A) Kaplan Meir Curve Showing Similar PFS in the Two Compared Periods (B) Kaplan Meir Curve Showing Similar OS in the Two Compared Periods

PFS in the two periods (p<0.015). Maritime Insurance Trust beneficiaries (MITB) had shorter (p=0.01) PFS in the later observation period compared to the other trusts' beneficiaries.

OS was available for 111 (n=52 before 2010; n=59 after 2010) patients. As shown in Table 3 and in Figure 1B, there was no difference (p=0.96) regarding OS between the two periods (13.70 [9.61-17.79] vs. 11.08 [7.74-15.92] months, respectively). Neither gender nor age at diagnosis nor insurance provider was related to shorter OS. On the contrary, higher PS and SCLC histology were associated with shorter OS (p<0.001 and p=0.013, respectively) only in the first period of observation.

Discussion

This study aimed to assess whether the health outcomes of advanced lung cancer patients have changed during the financial crisis era in a specialized oncology center in Greece.

The rationale supporting the choice of 2010 as the cutoff point was based on available literature and economic data. 2010 is widely assumed by researchers as the tipping point in Greece's healthcare expenditure

Table 3. Overall Survival, Months (Median [95%CI]), According to Enrollment Period

	<2010	>2010
Overall	13.70 [9.61-17.79]	11.08 [7.74-15.92]
Gender	P=0.91	P=0.72
Male	15.60 [9.72-21.48]	11.50 [10.14-12.87]
Female	13.70 [9.09-18.31]	15.57 [11.45-19.69]
Performance status	p<0.01	p<0.182
0	21.23 [5.00-37.46]	15.00 [5.00-25.00]
1	13.13 [5.93-20.33]	10.50 [9.60-11.40]
2	9.73 [9.52-9.95]	6.80 [0.00-16.28]
3	5.40 [5.40-5.40]	4.10 [2.50-5.70]
Age at diagnosis	P=0.72	P=0.47
<65	12.50 [6.34-18.66]	11.67 [6.26-17.08]
≥65	16.20 [10.88-21.52]	12.80 [6.11-19.49]
Histology	P=0.013	P=0.973
NSCLC	15.93 [10.25-21.61]	11.50 [6.70-16.30]
SCLC	9.73 [7.50-11.97]	12.80 [6.74-18.86]
Insurance provider	P=0.311	P=0.174
OGA	15.60 [2.60-28.61]	43.67 [6.38-80.96]
IKA	13.27 [7.71-18.83]	12.80 [6.36-19.24]
ON	8.00 [8.00-8.00]	5.030 [3.77-6.29]
OAEE	21.23 [21.23-21.23]	8.20 [0.00-18.88]
Other	16.20 [5.39-27.01]	9.67 [1.28-18.06]

[16-18]. This assumption is based on the fact that the consequences of the financial crisis had not been largely perceivable until late 2010, when Greece signed the first Memorandum of Understanding and measures of reduction of health spending began to be implemented [19]. Between 2009 and 2014, expenditure on healthcare decreased by more than 25%, average wages decreased by 20% and unemployment increased from 9.6% to 26.5% [8], while Greece witnessed a 29% drop in its gross domestic product (GDP) {Karanikolos, 2016 #2439}. Health care spending was drastically reduced from its peak 9.56% of the GDP in 2010, to 7.95% by 2014 [20] or from 9.85% to 8.29% according to the national statistical authority [21]. In a similar way, the 2nd health region of Greece, where the reference hospital is located, underwent substantial budget cuts after 2010 and until the end of the crisis, which affected our institution as well [22].

The fact that no differences in survival measures – namely OS and PFS - were noted in our institution between the two time periods, despite the presumed effects of the recession, is a matter of debate. Previous local research in the field yielded similar results with the researchers finding no significant changes on the PFS and OS of lung cancer patients before or after the financial crisis, setting 2008 as a benchmark year [9- 23]. One might argue that this is to be expected, as no significant changes have been noted in the management of these patients between the two time periods in relation to disease specific therapy [14]. As for availability of treatment is concerned, national statistics show significant cuts in pharmaceutical spending during the crisis [20]. However, a recent study from Greece regarding advanced lung cancer targeted treatment in the crisis era, showed that despite restrictions in the reimbursement policy patients still gained access to treatment through parallel national programs, while any temporary unavailability of treatment was not substantial enough to affect the anywise dreadful prognosis of the disease [8].

It can also be speculated that tertiary care has not been compromised by the crisis in contrary to primary care [19]. Therefore, the fact that no differences on survival were noted for the specific disease and time frame, does not exclude that the crisis might not have impacted on other aspects of public health, nor that the quality of care has not been compromised. Further research is warranted to address these questions.

The potential effect of the patients' health insurance provider on prognosis is of great interest. According to Greece's social insurance model, at the time the study was conducted, every employee was obligatory insured to a specific provider (e.g. maritime workers to Maritime Insurance Trust (ON), farmers to Agricultural Insurance Trust (OGA), freelancers to Social Insurance Trust (IKA), medical and health workers to Health Workers Insurance Trust (TSAY) etc. It has been argued that patients received different benefits according to their provider (e.g. some providers like IKA or National Bank Insurance Trust (TYPET) had their own hospitals thus allowing better access to health services). In addition, professional exposure to harmful substances, education, nutrition or other imponderable factors could be masked behind the provider (ON, OGA, and TSAY). Unfortunately, this information is hindered due to the unavailability of detailed and easily accessible medical records. This is a matter that needs to be addressed in the future.

Performance status was found to affect prognosis. The highest the PS the worse the PFS and OS. This is an expectable finding, as it makes sense for a patient presenting at a poorer clinical condition to have a worst prognosis. It is well known that these patients cannot tolerate chemotherapy, have more disease or treatment related complications, longer hospital stays and overall higher mortality and morbidity rates [24].

As far as the advantages of this study are concerned, caution was undertaken to avoid all possible confounding factors that could cause misinterpretation of the results, by strict adherence to the research protocol. The population of the first observation period had similar baseline characteristics with the population of the second observation period, except for more NSCLC cases enrolled after 2010 (Table 1). Disease specific therapy and demographics were also the same, thus allowing the assumption that the population comprising the two groups is practically identical and suitable for comparison.

Nevertheless, the study carries several limitations, although efforts were made to address most of them: Firstly, this is a retrospective single-center study thus inferences about nationwide advanced lung cancer survival in Greece in the time of crisis cannot be drawn with certainty from current data, while the study's limited sample size may not address all variables in a decisive manner. The population of the study also might not be representative of the general Greek stage IV lung cancer population, although Metaxa Hospital is probably the largest cancer hospital in Greece and accepts referrals from all over the country. In addition, due to the study's retrospective character and cross-sectional insight into the problem any correlation of the financial crisis to the patients' health outcomes should be made with caution as confounding factors, that could not be controlled or predicted, may have penetrated. One might also argue that the selection of a cutoff point other than 2010 may have changed the results the study, however, as already explained, the consideration of 2010 as the limit between the pre- and the crisis era has been widely adopted by researchers [16-18]. Finally, OS and PFS may be suboptimal indicators of financial crisis influence on cancer patients' health, although they have been similarly used in literature [23].

In conclusion, in our institution OS and PFS of stage IV wt NSCLC and SCLC patients did not differ significantly between the pre-crisis and the financial crisis era, using 2010 as a cutoff point. The insurance provider however seems to affect health outcomes in our institution, with MITB beneficiaries having shorter PFS in the second observation period compared to other trusts. This fact may imply inequities between beneficiaries according to their provider, which in turn compromised the quality of received care, thus warrants prospective research. Our findings are especially relevant nowadays, as the upcoming

forecasted recession due to COVID-19 pandemic is once again expected to affect Greece more than any other economy in the Eurozone. This old paradigm could serve as a guide to policy makers as to the proper allocation of health resources and mitigation strategies. It seems that tertiary care is not that affected by recessions and resources probably need to be allocated to primary healthcare and equity amongst healthcare beneficiaries.

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K.M, C.K, E.R.

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K.M, I.K, M.P, D.T, Z.S, A.T.

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RESEARCH ARTICLE

An Asian Perspective of the Management of COVID-19: the Asian National Cancer Centers Alliance Led Regional Comparison

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Abstract

Objective: To describe how the Asian National Cancer Centers Alliance (ANCCA) members preserve high standards of care for cancer patients while battling the COVID-19 pandemic and to propose new strategies in the Asian Cancer Centers' preparedness to future pandemics. **Methods:** A 41-question-based survey was developed using an online survey tool and conducted among 15 major Asian National Cancer Centers, including 13 ANCCA members. Direct interviews of several specialists were conducted subsequently to obtain additional answers to key questions that emerged during the survey analysis. **Result:** Institution/country-specific results provided a strong insight on the diverse ways of managing the pandemic around Asia, while maintaining well-balanced cancer care. Pragmatic strategies were put in place in each NCC hospital, including zoning and intensive triage depending on the pandemic impact. Distancing strategies and telemedicine were implemented in different capacity depending on the national healthcare system. In addition, there was a diverse impact on the manpower and financial aspect of cancer care across surveyed NCCs relating to magnitude of the pandemic impact on the country. **Conclusion:** The priorities nevertheless remain on maintaining cancer care delivery while protecting both patients and health care workers from the risk of COVID-19 infection. The role of a think-tank such as ANCCA to help share experiences in a timely manner can enhance preparedness in future pandemic scenarios.

Keywords: Asia- cancer- cancer center- Coronavirus- COVID-19- patient

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Introduction

The current coronavirus pandemic has created a global crisis. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which caused Coronavirus disease 2019 (COVID-19), is a novel coronavirus first detected in Wuhan, China in December, 2019 [1]. As of 13-July 2020, over 570,000 people have died from COVID-19 related disease with more than 13 million people being infected globally. Of them, 3 million cases and over 70,000 deaths have been described in the Asia region, representing a global share of 23.21% and 12.42% for incidence and mortality, respectively [2]. Report from WHO-China Joint Mission on COVID-19 showed that comorbid conditions such as cardiovascular disease, diabetes, hypertension, chronic respiratory disease, and cancer lead to poor clinical outcomes and higher mortality rates compared to patients without comorbid concerns [3]. The immunocompromised status of cancer patients caused by both the malignancy and anticancer therapies (chemotherapy, surgery, and radiotherapy) increases the likelihood to develop severe complications of COVID-19. Growing evidence from several countries particularly China, Italy, and United Kingdom have reported cancer as a major risk factor for adverse outcomes of and death from COVID-19 [4-6].

Rapid spread and epidemiological novelty of coronavirus infection have brought unprecedented challenges to the healthcare systems globally. Healthcare professionals have been urged to re-organize healthcare systems, sometimes without sufficient scientific evidence available at the beginning of the pandemic. Cancer providers need to alter care delivery models in order to handle the COVID-19 crisis as well as to protect patients without compromising cancer outcomes. Over time, various strategies have been initiated and proposed, including the countrywide strategic preparedness and response plan suggested by WHO; access to resources specific for cancer patients with COVID-19 provided by several organizations including the Union for International Cancer Control (UICC); and research recommendation and initiatives were made available on International Agency for Research on Cancer (IARC) and the United States National Cancer Institute (NCI) websites.

The Asian National Cancer Centers Alliance (ANCCA) was established in 2005 as an initiative to embark together to fight against cancer. With 14 leading cancers institutions in Asia (mostly National Cancer Centers (NCC) recognized by their respective Ministries of Health), ANCCA is the official group of leading cancer centers in Asia that serves as hub and driver to promote collaboration among ANCCA members as well as with multiple stakeholders in cancer care and prevention [7]. The COVID-19 pandemic triggered a regional collaborative effort led by ANCCA member countries, namely NCC-China, NCC-Indonesia, NCC-Japan, NCC-Korea, NCC-Mongolia, NCC-Singapore, NCC-Vietnam, as well as Institut Kanser Negara (NCI-Malaysia), National Cancer Institute (NCI)-Thailand, NCI-Turkey and Hacettepe Oncology Institute (NCI-Turkey-HOI), Tata Memorial Centre (India-TMC), Nepal Kathmandu Cancer Center (Nepal-KCC), Shaukat Khanum Memorial Cancer Hospital & Research Centre (Pakistan-SKCC), and with the collaboration of two other Asian institutions from Iran and Myanmar (Iran Tehran Cancer Institute (Iran-TCI) and Myanmar Yangon General Hospital (Myanmar-YGH), to summarize, compare and discuss the different strategies in managing cancer-care that were tailored based on country's pandemic preparedness, state of epidemic curve, political and economic status of each country.

Among the ANCCA member countries, the emergence of COVID-19 varied in extent and time, represented by various dates of national emergency declaration, depicted from 24-January 2020 for China to 7-April 2020 for Japan (Figure 1). One trend that became apparent was the prompt governmental action by early responders (January – February) to the pandemic (by time of declaration: China, Mongolia, Malaysia, Singapore, Iran, and Korea), highlighted by the date of emergency declaration and occurrence of COVID-19 cases in each of these countries. In general, the course of COVID-19 pandemic and the actual encounter of COVID-19 patients in NCCs defined the context in which each institution developed and implemented its plans (Table 2). Adding to the complexity to manage the circumstances and adapt its strategies to re-organize the delivery of cancer care while going through the pandemic management were other factors such as the geographic location; status of emergency state declaration; country population; and population density or land area.

With the NCCs needing to handle challenges in adopting new ways of cancer delivery, the ANCCA facilitated the sharing of strategies to preserve high standards of care through regular video conferences among members and making available resources/materials related to COVID-19 on the ANCCA website. This paper is an extension of the sharing efforts and describes actions taken by thirteen ANCCA members and two collaborative members to re-organize cancer services by balancing the COVID-19 specific implementation strategies.

Materials and Methods

Through regular interactions, ANCCA members decided to join forces in response to the COVID-19 pandemic by designing and distributing an online survey to 14 ANCCA members, and to 5 non-members cancer institutes in the Asia region. The aim of the survey was to assess the short- and longer-term impacts of the pandemic on Asian cancer centers' activities as well as implemented strategies and countermeasures through a set of 41 questions divided into 6 categories.

The online survey tool was used to collect both open-ended and closed-ended questions (multiple choice and rating scale choice questions) to congregate relevant data from respondents. The qualitative and quantitative data were then used to analyze for trends of strategies adopted by ANCCA members and other Asian cancer centers.

Questions were distributed into 6 major categories: impact at the national and at the institutional level; hospital

preparedness; strategies in place or countermeasures; triage; zoning, and repurposing. Survey topics also included the impact of the pandemic on cancer treatment and cancer care, such as distancing measures, online systems and quality of life (QOL) management. The area of clinical trial was also included for cancer centers running clinical trials before the pandemic to understand the challenges the centers experienced in conducting clinical trials (including those related to COVID-19). The specific aspect of the financial impact of COVID-19 on each institution was also ascertained from all participating members.

Quantitative and qualitative results were analyzed and sorted to allow most meaningful comparison among cancer centers. The contribution of specialists with specific knowledge and expertise from a wide range of departments, including infection control, human resources, finances, and oncology field played an essential role in extracting in-depth information on challenges and ways of addressing the pandemic.

Thirteen ANCCA members and 2 non-ANCCA Asian major cancer centers responded to the voluntary survey, providing thorough insight on the impact of the pandemic, their countermeasures as well as short- and long-term strategies. Response collection occurred between 22-May 2020 and 2-June 2020 for ANCCA members and between 8-June 2020 and 14-June 2020 for other cancer centers in Asia, representing in total centers from 15 countries in the region. Subsequent direct interviews of specialists were conducted to obtain additional answers to open-ended questions that required for input as assessed during the survey analysis.

Results

Pandemic in Asia: Overall status

Among participating countries, the emergence of COVID-19 varied in magnitude and with time, reflecting the different timing of each government's decision to declare COVID-19 as national emergency (Figure 1). Two trends could be extracted from WHO [8] data comparing COVID-19 weekly incidence of participating countries as of 19-June 2020 (cut-off date) (Figure 1). The first was based on the number of weekly cases, segregating countries into four categories: "high" incidence (>20,000 weekly cases at peak); "higher middle" (between 4,000 and 8,000 cases weekly); "lower middle" (between 500 and 3,000 cases weekly at peak); and "low" (below 100 cases weekly at peak).

The second trend observed could also be classified in 3 different patterns: one single peak observed (per time of peak occurrence: China, Korea, Thailand, and Japan, seemingly having overcome the first wave of COVID-19); one peak followed by less prominent decrease (per time of first peak occurrence: Turkey and Singapore still struggling with rising curve); and a third group of countries with later start, a peak that did not reach at cut-off date (per time of occurrence start: Indonesia, India, Pakistan, and Nepal currently facing an ostentatious growth in the number of COVID-19 patients). The second trend was not applicable for countries with low COVID-19 incidence (i.e. Mongolia, Myanmar and Vietnam). The course of COVID-19 pandemic in each country (Figure 1) as well the actual encounter of COVID-19 patients at the cancer centers (Table 2) define the context and circumstances in which each institution took countermeasures to re-organize the delivery of cancer care while going through the pandemic.

Regional leadership and strategies in place or implemented (including staff management)

Despite the unpredictability of the pandemic, most participating cancer center adapted with immediate actions, partly due to availability of infection control measures and management practices, with 13 (87%) cancer centers confirmed the existence of a specific infection control dedicated department in place, and 8 (53%) confirmed the presence of dedicated staff. As a concrete action plan, most centers developed or updated guidelines or contingency measures in response to the pandemic. Eleven (73%) centers developed or updated guidelines related to infection management as countermeasures to the pandemic. NCC-Singapore's programs are worth highlighting: high level of preparedness through the existence of the Disease Outbreak Response (DORS) taskforce, regular review of its operational manual according to national and international guidelines, as well as conducting pandemic response exercises within the campus. Two other concrete examples are from NCC-Korea with a system termed Drug Utilization Review (DUR) which allows the legal access of people's overseas travel history, as well as a screening processes (with instructions on screening clinics and booths at every entrance and every visitor) in place; and Myanmar-YGH's new guidelines for the use of blood and blood products.

In addition, as a response to the pandemic, 11 (73%) centers took prompt and sustained educational initiatives directed at healthcare professionals and cancer patients, showing leadership in the cancer field in the Asia region with an obligation for educating the staff and public. India-TMC and NCC-Indonesia started regular webinars for healthcare professionals on 21-March 2020 and 22-April 2020 respectively [9-10]. Pakistan-SKCC launched a resource library and conducted information sharing sessions for healthcare providers starting from February 2020 [11] and published a COVID-19 guideline on 10-April 2020 [12]. NCC-Vietnam organized a weekly online consultation program ("Things to know for cancer patients during the COVID-19 pandemic"), as of 14-April 2020 [13]. NCC-China enhanced the health education for cancer patients and the public on personal protection measures and principles of cancer care during the pandemic. In Korea, the Korean Cancer Society and NCC-Korea made a press release on 29-April 2020 on the "Recommendations for cancer patients based on COVID-19 situation" [14].

As another evidence of regional leadership, 8 cancer centers (53%, India-TMC, NCC-Japan, NCC-Vietnam, Iran-TCI, Myanmar-YGH, Nepal-KCC and Pakistan-

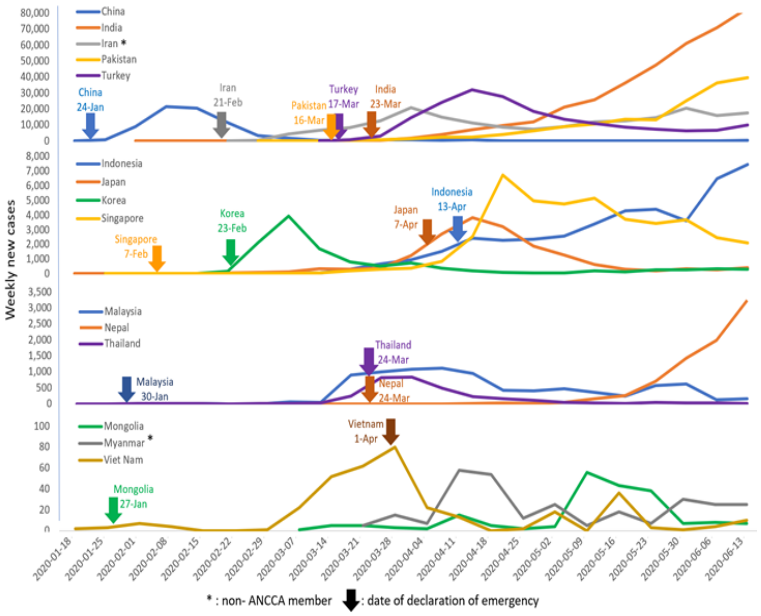

Figure 1. Transition of COVID-19 Case Based on WHO Data among Responders and Date of National Declaration of Emergency

SKCC) actively participated by contributing their eminent speakers to share their experience and expertise in virtual international meetings and symposium to combat COVID-19 for the benefit of other institutions or countries.

Staff management (including social distancing) was also a key focus of most centers, with respectively 9 (60%) and 11 (73%) centers implementing "working from home" and "virtual meetings" (Table 1). Decrease of staff was the norm, while increase of staff was also observed, partly due to staff re-allocation related to COVID-19 preparedness and management of triage; pre-screening; screening activities; as well as the treatment of COVID-19 patients, in about half the respondents (7 responders (54%)).

It is noteworthy that NCC-Indonesia implemented workforce rearrangement strategy in order to protect staff (especially > 60-year-old and with comorbidities) and to ensure successful implementation of social and physical distancing. India-TMC also took similar exemplary measures to address the psychological impact of the pandemic on healthcare workers through timely communication with all cadres of staff regarding preparedness, paid-leave for high-risk staff members (elderly people, people with co-morbidities or with immunosuppressive treatment and pregnant women); rotation of staff (2/3rd on-site working and 1/3rd working from home to ensure availability of enough numbers in case of mass exposure and quarantine); and arrangement of transport for staff during the lockdown. To secure proper care, Polymerase Chain Reaction (PCR) tests for staff suspected with COVID-19 was mandatory at 9 centers (60%). NCC-Indonesia, NCI-Turkey-HOI, and Nepal-KCC implemented serologic/immunity test as a screening tool to select patients and healthcare workers who must take PCR-tests [15].

Triage (including guidelines), zoning, repurposing and material shortage – Hospital level

To combat the pandemic, all cancer centers adopted ad hoc short- and long-term measures from pre-screening to treatment or re-orientation of their cancer patients, while managing with the shortage of material (personal protective equipment (PPE), including masks, hand sanitizers, gowns, as well as oncology drugs, COVID-19 related drugs, other drugs, blood products, medical devices, and laboratory testing). Pre-screening measures included the travel history information system (NCC-China, NCC-Korea, NCC-Vietnam) and the massive COVID-19 screening and triage at the entrance (NCC-China, India-TMC, NCC-Korea, NCC-Indonesia and NCC-Singapore). As concrete examples, NCC-China closed all entrances except the main entrance, and NCC-Singapore established a fever screening clinic with COVID-19 swabbing capabilities and redirecting COVID-19 cancer outpatients to Singapore General Hospital. At NCC-Vietnam, early implementation of contingency plan and social distancing, as well as screening regulations (based on strategies taken by Central Government) eased the burden, facilitating COVID-19 prevention in the hospital.

More than half of responding centers (8 centers, 58%) had actually encountered and mostly treated COVID-19 patients, while 6 centers (43%) were COVID-19-free at the time of the survey (Table 2). The centers with major impact of COVID-19 were India-TMC and Pakistan-SKCC, dealing mainly with cancer patients with COVID-19, while NCC-Japan, NCI-Turkey-HOI, and Myanmar-YGH dealt mainly with COVID-19 patients from the general population. NCC-Japan was an outlier NCC, having to open a specific ward and treat 15 non-cancer patients as a response to the "special COVID-19 functioning hospital" by the Ministry of Health and Welfare from 14-April to 29-May 2020, reallocating up to 40 staff at the peak and

Table 1. Distancing Strategies in the Cancer Centers to Decrease Physical Contact among the Staff and the Patients

Institution	Less family and visitors	Staff virtual meetings	Staff working from home	Online consultation	Non-urgent surgeries suspended	Reschedule surgeries	Reschedule cancer screening and prevention	Reschedule chemotherapy	Reschedule radiotherapy	Delay other aspects of treatment	Refer patients to other hospital	Refuse new patient visits	Refuse second opinion	Total
NCC-China	○	○	○	○	○	○	○	○	○		○			10
NCC-Indonesia	○	○	○	○	○	○	○	○	○	○	○			11
NCC-Japan	○	○	○	○	○	○	○	○	○	○	○			11
NCC-Korea	○	○		○	○	○	○	○	○	○	○			10
NCC-Mongolia	○													1
NCC-Singapore	○	○	○	○	○					○	○		○	8
NCC-Vietnam	○	○	○	○	○	○	○	○	○					9
NCI-Thailand	○	○	○	○	○	○	○							7
NCI-Turkey-HOI	○	○	○	○	○		○							6
India-TMC	○	○	○	○	○		○			○				7
Nepal-KCC	○	○		○	○	○	○	○	○	○	○			10
Pakistan-SKCC	○	○	○	○	○	○						○		7
Iran-TCI	○	○		○	○	○		○	○					7
Myanmar-YGH	○	○		○	○	○		○	○					7
Total	14	13	9	13	13	10	9	8	8	6	6	1	1	

implementing 4 shifts to avoid contamination, all based on prior experience of infectious disease management. It is also noteworthy that Pakistan-SKCC contributed to the national effort against the coronavirus and made the strategic decision to enable free testing and treatment for COVID-19 cancer and non-cancer patients unable to afford it [16].

The actual material shortage status varied among centers, less impacting for centers not having encountered COVID-19 patients, except for NCC-Mongolia (experiencing shortage of oncology drugs and medical devices due to shipment delay) and Nepal-KCC (with shortage of PPE, cancer and non-cancer drugs as well medical devices and other equipment). For centers experiencing COVID-19 patients, a shortage of PPE, swabs, tubes for reagents, isolation gown, cancer and non-cancer drugs as well as of medical devices was noted at various levels depending on the centers. The highest impact of shortage was on PPE, and also reagents for PCR testing (NCC-Japan, NCC-Indonesia), and Rapid Detection Kit (RDT) (NCC-Indonesia). To overcome the pandemic, Pakistan-SKCC (the most affected institution) as well as India-TMC and NCC-Indonesia took initiatives such as accepting donations from philanthropic organisation or government while NCC-Singapore prevents the shortage of PPE through developing a strict PPE guideline for optimal protection of staff and patients. As a specific case, NCI-Turkey-HOI did not experience any specific shortage despite the high number of COVID-19 patients in the institution.

Patient care: impact on treatment and online systems – Hospital level

Aiming to preserve high standards of care for patients with cancer, participating centers adapted to their healthcare environment and needs in different ways (Table 1). In addition to decreasing contact through exposure to family members and visitors, implemented by all centers (100%), various aspects of cancer treatment were modified, with a non-negligible impact on both the institution and patients and their families. Worth noting is the postponement of non-urgent surgeries, rescheduled surgeries, cancer screening, chemotherapies or radiation therapies taken respectively by 13 (93%), 10 (71%), 9 (64%), 8 (57%) and 8 (57%) centers, treatment modifications highlighted by several members as case-by-case decision based on prioritization. In order to minimise the impact on cancer treatment, respondents adopted different strategies, such as: for patients preparing to be admitted, NCC-China routinely recorded symptoms potentially associated with COVID-19, such as fever and cough through mandatory routine blood tests and high-resolution computed tomography scans of the lungs. India-TMC did not modify its treatment protocols except rescheduling the post-treatment follow-up and selecting less myelosuppressive chemotherapy for palliative

Table 2. Number of COVID-19 Positive Treated in the Cancer Centers and Zoning Plan for COVID-19 Patients

	Institution	# COVID-19 Positive cancer patients (1)	(1) of which % treated at institution	(1) of which % referred to other hospital	#Treated general population	Zoning plan for COVID-19 patients		
						Single entry / exit	Separate entry / exit	Dedicated ward
No encounter with COVID-19 patients	NCC-China	0	N/A	N/A	0		○	○
	NCC-Korea	0	N/A	N/A	0		○	○
	NCC-Mongolia	0	N/A	N/A	0			○
	NCC-Vietnam	0	N/A	N/A	0		○	
	NCI-Thailand	0	N/A	N/A	0	○		○
	Nepal-KCC	0	N/A	N/A	0		○	
Encounter with COVID-19 patient (s)	NCC-Indonesia	5 (100%)	4 (80%)	1 (20%)	0		○	○
	NCC-Japan	2 (100%)	1 (50%)	1 (50%)	15		○	○
	NCC-Singapore	3 (100%)	2 (67%)	1 (33%)	0	○		
	NCI-Malaysia	1 (100%)	0 (0%)	1 (100%)	0	○		
	NCI-Turkey-HOI	7 (100%)	7 (100%)	0 (0%)	350			○
	India-TMC	314 (100%)	264 (84%)	50 (16%)	0	○		○
	Myanmar-YGH	1 (100%)	1 (100%)	0 (0%)	10		○	
	Pakistan-SKCC	231 (100%)	67 (29%)	164 (71%)	21		○	○

Table 3. Proportion and Types of Online Consultations at each Cancer Centers before and During the Pandemic

Institution	Prior system in place for online consultation	% Online consultation prior to pandemic	% Online consultation during pandemic	Types of online consultation				Notes
				Telephone	Video	Chat-based	E-mails	
NCC-China	○	5%	70%	○		○		System in place, free of charge, chat-based system on NCC website
NCC-Indonesia		0%	10%		○			Online consultation available but outside of the scope of insurance coverage
NCC-Japan		0%	8%	○				Approval of online consultation by MHLW on 1-Apr, allowing patients to pick up their drugs at pharmacies closed to their house
NCC-Korea		0%	3%	○				Online (telephone) consultation legalized on 24-Feb
NCC-Mongolia	○	0%	0%					National insurance scheme system in place for online cons ultation, not applied yet due to no COVID-19 transmission
NCC-Singapore	○	0%	10%	○	○			Secure system recently developed for consultation and charging
NCC-Vietnam		0%	90%	○	○			Common unofficial practice of telephone consultation between patient and physician, not paid therefore not recorded
NCI-Thailand		0%	5%	○	○	○		
NCI-Turkey-HOI		0%	25%	○				
India-TMC		10%	30%	○	○		○	
Nepal-KCC		60%	80%	○			○	
Pakistan-SKCC	○	0%	60%	○	○			Online credit card mobile billing application
Iran-TCI		20%	40%	○	○			Online consultation applied only at palliative care services, through the use of personal phone number
Myanmar-YGH		30%	50%	○		○		Booking ahead, Viber group, Facebook page

indication; while NCC-Indonesia and NCC-Vietnam rescheduled suitable treatments making sure not to compromise the treatment objectives. Two exceptional cases were NCI-Turkey-HOI, with no modification in cancer treatment, and NCC-Mongolia, with zero local transmission as of 22-May 2020 (time of filling the survey), which only restricted the number of family members and visitors.

Focusing on the "telemedicine" aspect, 13 centers (93% of participants) implemented online consultation in various ways (Table 3). NCC-Vietnam made the most significant change: from zero before to 90% during the pandemic. NCC-China, India-TMC, Nepal-KCC, Iran-TCI, and Myanmar-YGH had already implemented the online consultation system prior to the pandemic, which allowed for a smoother implementation. In China, the national health and insurance system in place allowed cancer patients from all over China to get free access to online free-of-charge consultations including instructions on taking medication and cancer-related symptoms management. In Japan, the Ministry of Health and Welfare approved Emergency Countermeasures for COVID-19 on 7-April 2020 which allowed NCC-Japan to implement telemedicine [17], still in application at the time of this manuscript submission. Another fast shift was in NCC-Singapore's implementation of a secure system for consulting and charging.

On the quality of life perspective (Table 4), most centers took initiatives: NCC-Singapore allowed video-conferencing for patients and their families, as well as between medical teams and relatives to update on patient's conditions. NCC-Japan and NCI-Turkey-HOI, smoothened the prescription process to facilitate patients to obtain drugs through online consultation without the burden of an hospital visit. NCC-China, NCC-Vietnam and India-TMC undertook similar approaches to overcome COVID-19 impact on patient's wellbeing by providing food or nutrition support, psychosocial support, as well links with web-based support group meetings. NCC-Japan provided web-support, allowing home exercise for cancer

Table 4. Initiatives Related to Quality of Life of the Patients

Institution	Specific actions to maintain cancer patient quality of life	
	Outpatient support	Inpatient support
NCC-China		Education on the nutrition by nurses, physical activity and psycho-oncology support for inpatients
NCC-Indonesia	1. Provision of online consultation for palliative patients, conducted by palliative doctor as alternative solution for home care/visit that cannot be held during partial lockdown 2. Provision of medicine refill through electronic prescription following online consultation	Psychology support for suspected or confirmed cases of COVID-19 patients by clinical psychologist to facilitate patients' acceptance on their illness, reduce patients' anxiety, and provide motivation to improve patient's condition
NCC-Japan	1. Information sharing about home exercise for physical activity 2. Prescriptions made available at local pharmacy after online consultation with physician	
NCC-Korea	1. Provision the home hospice visit service to the patients as usual with medical staffs only (no volunteers, social welfare workers, etc.) 2. Maintain the highest sanitary conditions to the visitors by applying strict infection control policy	Maintaining the provision of palliative care service while minimizing group meeting among patients and the number of responsible staffs (e.g. excluding volunteers and maintaining only medical staffs)
NCC-Mongolia	No particular action needed to limited impact of COVID19	Introduction of dedicated hours and restricted access for the visitors and family members at the hospital
NCC-Singapore	1. Support to inpatient medical teams by palliative physician 2. Video consultation for community care team for outpatients for management of pain and other quality of life issues	1. Video conferencing for patients to stay in contact with their family 2. Communication between medical team and relatives to update conditions as visitors are not allowed in the wards
NCC-Vietnam	Tele-consultation open session on the hospital website and Facebook about nutrition and psycho-oncology support for patients	
NCI-Turkey-HOI	No need for prescription and coming to hospitals	
India-TMC	1. Provision of food and accommodation 2. Travel arrangement 3. Linking them with the volunteers for psychosocial support 4. Support group meetings using platforms like zoom	1. Provision of food to the relatives 2. Extending the stay for those who were outstation patients
Nepal-KCC	Provision of free vehicle facilities for cancer patients and hand sanitizer to all	
Pakistan-SKCC	Everyday telephonic updates for relatives. Video calls between patients and relatives	
Iran-TCI	Palliative care team (volunteers) in some region support patients/ virtual consultation by palliative medicine specialist	Virtual tumor boards about difficult patients
Myanmar-YGH	Provision of bed allocation 3 feet apart/by marking waiting area for social distancing, provision of hand washing facility, restriction of patient attendance	Provision of good nutrition support and palliative care for all inpatients

patients.

Clinical trials

Research-wise, the pandemic also highly impacted 8 of the 9 centers (89%) who were actively participating in clinical trials prior to the pandemic, with NCC-Vietnam as an exception, not much impacted due to short social distancing period and controlled outbreak in Vietnam. Most industry-led trials were delayed, with major impact on patient recruitment and visits on 7 centers (78%), and on the overall timeline for 6 centers (67%) (Table 5).

Relevant actions and countermeasures included: rapid identification of life-saving clinical trials for immediate approval to continue; deployment of clinical trial coordinators to triage and screening when patient recruitment was reduced (NCC-Singapore); telephone-call based follow-up for trial patients and sending drugs by courier services (India-TMC). By contrast to industry-lead clinical trials, NCC-Japan reported that the impact on investigator-led clinical trials was limited.

Acting as Asian leaders in their field, several ANCCA members also actively contributed to knowledge on COVID-19: NCC-Singapore's collaboration on a clinical trial on Virus specific T cells for COVID-19, India-TMC evaluating cancer outcomes in patients with COVID-19, NCC-Japan and Pakistan-SKCC respectively participating in a nationwide Avigan observational study and a WHO COVID-19 vaccine clinical trial.

Impact on NCCs' departments (including manpower and financial impact)

National Cancer Centers and Institutions from ANCCA are established as leading cancer centers in the region, hosting a broad range of cancer related services to maintain a comprehensive cancer care, cancer control activities, and research on cancer. Clinical and education services and research activities are core activities for all participating centers, besides the other cancer-related departments as depicted in Table 6. All participating centers, even the 6 centers which did not experience COVID-19 patients, were affected by the pandemic. Most highly impacted departments were the hospitals (all centers impacted,

Table 5. Impact of COVID-19 Pandemic on Clinical Trials

Institution	Patient Recruitment or Enrolment	Providing investigational product to patients	Patients' visits	Overall quality	Overall completion timeline	Participation to new clinical trial related to COVID-19
NCC-China	○	○	○		○	N/A
NCC-Japan	○		○		○	Avigan observational study. 14 out of 15 COVID-19 patients at NCC were enrolled. This study is a nation-wide study
NCC-Korea	○		○		○	N/A
NCC-Singapore	○	○	○		○	Collaboration on clinical trial on Virus specific T cells for COVID-19
NCC-Vietnam						N/A
NCI-Turkey-HOI	○					N/A
India-TMC	○	○	○		○	Cancer outcomes in patients with COVID-19 ongoing
Pakistan-SKCC	○		○			WHO COVID-19 Vaccine Trial
Iran-TCI			○	○	○	N/A

N/A, Not Applicable

respectively highly impacted and impacted somehow by 8 (57%) and 6 (43%) centers), education services and cancer screening and prevention (respectively 10 centers (71%) and 7 centers (50%) had to shut down or were highly impacted). In NCC-Vietnam, the social distancing regulations, even though for a limited period of time, created a huge burden on internal resource requirement and operational coordination, with a drastic increase of patients (new and existing) at the imaging diagnostic department, resulting in subsequent increase of workload for the whole department following the lifting of social distancing measures.

Financial consequences in most departments caused by the pandemic were significant, estimated to be around 30% loss in comparison with the previous year, depending on the institution. Countermeasures were limited or non-existent for most cancer centers at the time of completion of the survey. COVID-19 related expenses were diverse, including reduction of outpatient and inpatient visits, staff and medical equipment shortage after complete or partial lockdown declared in all participating countries, independently from the actual occurrence of cases in the country or the institution. Striking examples are NCC-Vietnam and NCC-Mongolia which were highly financially impacted despite low number of cases in the country. NCC-Vietnam experiencing a 30% financial loss due to triage and reduction of patient visits in addition to the increased budget spent on extra-hours to screen staff and visitors, to quarantine suspected cases and other related measures. Another costly investment worth pointing out was the new fever and triage area in NCC-Singapore, and cost related to the increased lab capacity

Table 6. Impact of COVID-19 on each Institution

Institution	Hospital	Cancer Screening and Prevention	Research Institute	National Cancer Control Department	Public health	Educational services	Central Laboratories / PCR machines	Overall impact on workforce
NCC-China	**	**	***	*	N/A	**	***	-
NCC-Indonesia	**	***	-	N/A	N/A	***	**	↓
NCC-Japan	**	***	*	*	*	***	**	↓
NCC-Korea	*	*	*	*	**	**	*	↓
NCC-Mongolia	*	*	-	-	-	**	-	-
NCC-Singapore	**	*	***	N/A	N/A	**	**	↑
NCC-Vietnam	*	*	-	N/A	**	*	-	↓
NCI-Thailand	*	**	-	*	**	*	-	↑
NCI-Turkey-HOI	*	*	*	*	*	**	-	↓
India-TMC	*	***	**	**	***	*	-	↓
Nepal-KCC	*	**	*	*	-	-	-	↓
Pakistan-SKCC	**	N/A	-	-	N/A	**	-	-
Iran-TCI	**	**	*	**	**	**	**	↓
Myanmar-YGH	*	*	*	*	*	**	*	↓

*** Had to shut down; ** Highly impacted; * Impacted somehow; -No change; ↑Increase; ↓Decrease; N/ANot applicable

Table 7. The Way Forward [58-59]

Area of Focus	Strategies employed	Experience gained / Lessons learned
Crisis management and preparedness toward sustainability and longer-term preparedness	• Contingency plans • Implementation of new guidelines and standard procedures • Creation and update of guideline: Management of infectious disease on cancer care setting- current momentum • Crisis communication	- Sharing best practices among members - Logistic supports and availability of medicines, material and devices - Telemedicine implementation and national potential applications - Guidelines and criteria for patients requiring admission or self-quarantine to reduce risk of transmission - Role of media on awareness program and education
Emergency preparedness	• Triage at every entrance • Zoning area (single vs separate entry) with dedicated ward for suspected/confirmed cases	- Tracking of travel history / pre-screening - Screening booths - Separate routes for infected patients - Dedicated isolation ward (including ICU) - Simulation drills
Cancer patients' care (short term)	• Social distancing • Patient's QOL management	- Online consultation system - Booking by phone one day ahead of outpatient consultation - Transportation / travel arrangement for patients - Psychological support to improve patient's QOL - Transparent information to patients - Specific education on principle of cancer care during pandemic - Home exercise support - Managing patients' expectation based on their experience during pandemic - Family/caregivers support to cancer patients with COVID-19 infection
Cancer care continuum	Adaptation of treatment strategies (across cancer types and specific by cancer type)	- Modification on cancer protocol - COVID-19 testing to asymptomatic patients' prior treatment/procedure - Avoidance of delaying treatment/procedures to COVID-19 negative cancer patients - Increased capacity on remote diagnostic and treatment through optimization of digital technology - Single-room-one-patient policy for infected patients
Staff management	Caring for staff: address staff shortage and psychological support	- Transportation / travel arrangement for staff - Rotation of staff in shifts to avoid cross-contamination - Special care for staff with co-morbidities, taking immunosuppressive agents, and > 60 years old (e.g. paid leave)

Appendix 1. Cumulative COVID-19 Cases and Deaths (13-July 2020)

Country	Cumulative cases	Cumulative deaths
India	878,254	23,174
Iran	257,303	12,829
Turkey	212,993	5,363
Pakistan	251,625	5,266
China	85,568	4,648
Indonesia	75,699	3,606
Japan	21,868	982
Korea	13,479	289
Malaysia	8,718	122
Thailand	3,220	58
Nepal	16,801	38
Singapore	45,961	26
Myanmar	331	6
Mongolia	230	0
Viet Nam	372	0

in NCC-Indonesia (which was appointed on 15-April 2020 by the Regional government to provide PCR tests for COVID-19).

Discussion

NCC Leadership and strategies

National Cancer Centers around the world have the responsibility to balance the risk from delay in cancer diagnosis or treatment against the potential risk of COVID-19 exposure, mitigate the risk of disruptions to cancer care delivery during implementation of social distancing strategy, and manage the proper allocation of limited health care resources. Outbreaks of infection etiology, particularly those caused by a novel virus with no known treatment, may result in the interruption of medical care provided to patients with cancer and put them at risk for undertreatment in addition to the risk of being exposed to infection, which collectively could be a life-threatening event for patients with cancer [18].

ANCCA members have established a roadmap at the end of 2019 [7] with short-, mid-, and long-term goals to halt cancer increase and mortality rates in Asian countries by 2030. The pandemic, through its dramatic impact on society, and even further on cancer care, has opened doors to new collaboration and goals not originally specified. Such pandemic challenge faced by each and every country in the region has allowed ANCCA members to increase the speed and focus the goal of collaboration to decrease the impact of the pandemic on one of the most affected population: cancer patients and healthcare professionals. Shortly after the start of the pandemic, on 22-April 2020, the presidents of 3 NCCs (NCC-China, NCC-Japan and NCC-Korea) virtually gathered to share latest updates, followed by a virtual meeting attended by most members on 20-May 2020, to promote information sharing among ANCCA members through a survey addressed to each institution representative.

Managing cancer care through a pandemic was not new for 10 participating cancer centers (67%) which experienced one or two major coronavirus outbreaks in the region: Severe Acute Respiratory Syndrome (SARS) with a 2003 and Middle East Respiratory Syndrome (MERS), with a 2012 outbreak that have allowed several Asian countries to prepare for the pandemic, from a governmental as well as institution level management of the pandemic [19]. The participating countries of this study were respectively China, India, Indonesia, Korea, Malaysia, Mongolia, Thailand and Vietnam for SARS and Korea, Malaysia, Iran and Turkey for MERS [20] with Korea and Malaysia experiencing their third encounter this time since coronavirus in 2002.

The survey outcomes included the establishment of an infection control department and/or dedicated staff, which turned out to be in place prior to the pandemic for respectively 13 centers (87%) and 8 centers (53%), allowing the distribution of fast and relevant information to the community (healthcare workers, as well as patients) that are key to contribute to national, regional and international efforts to decrease the impact of the pandemic on cancer care.

The results of this study include lessons learned through very stringent actions for NCC-China and NCC-Korea, both tracking the travel history and symptoms of all individuals as well as performing a thorough screening at entrance of all employees.

Caring for staff strategies

Cancer care providers are at increased risk for coronavirus infection as chances of acquiring infection at workplace are high. Previous experiences of SARS and MERS outbreaks had shown that the rate of Coronavirus transmission among healthcare workers were significant, accounting for 21,07% [21] and 19,1% [22-23] of confirmed cases, respectively. Current data on COVID-19 case among healthcare providers are incomplete and very dynamic. However several studies have reported a high rate of COVID-19 transmission among healthcare workers since the onset of the outbreak [23-25]. This situation has led to substantial decrease of available staff due to self-isolation (staff was suspected of COVID-19 or household member developed symptoms).

The pressure of working under pandemic circumstances was augmented by staff's anxiety of the risk of personal contamination and extended work hours [25]. Having contact with confirmed cases of COVID-19 demonstrated as significant factors of high level of distress, experienced by 29-35% healthcare workers delivering care to SARS patients [26] and 26% of doctors involved in MERS care [27]. Past experience provided lessons that healthcare management team should put attention on staff's need of logistic and psychological support [23]. In NCCs of the participating countries, staff protection is one key focus of COVID-19 related strategies, including the implementation of staff virtual meeting and working from home policies to ensure social distancing approach; modification on treatment regimens and rescheduling of non-urgent treatment to reduce hospital

visits, and psychological support for staff dealing with suspected or confirmed COVID-19 cases.

Impact on patient care

Cancer center efforts to continue its operations and ensure the safety to resume elective procedures have been guided by standards published by international oncology associations, particularly ESMO, ASCO, NCCN, and American College of Surgeons. Patients prioritization and modification of cancer treatment protocols were implemented to reduce hospital visits and ensure the implementation of social distancing measures in order to minimize the risk of SARS-CoV2 transmission. Similar approaches have been taken by cancer centers worldwide, for instance oncology institutions under the legal entity of Cancer Core Europe (CCE) [28] and comprehensive cancer centers in US [29-31]. The strategy was effective to reduce the overall number of cancer patients admitted by 70-80% of the normal influx [28] and decrease the on-treatment patient volume (OPTV) by 25% in anticipation of the expected local COVID-19 peak [29].

The extent of social-distancing strategies implemented by NCCs are determined by government approaches to control pandemic at the national level. The population-level physical distancing measures and movement restrictions, often referred as "shut down" and "lock downs" were introduced in many countries, especially where community transition has led to outbreaks with near exponential growth [32]. Two different approaches to control COVID-19, namely suppression and mitigation were introduced and implemented in each country with varying extent. Suppression strategies aim to reach nearly complete suppression (reverse the epidemic spread to reproduction number (R) < 1 and establish population immunity once a vaccine becomes available) [28,33], while mitigation strategies aim to keep COVID-19 incidence consistently at the maximum levels acceptable in order to prevent overwhelming the healthcare systems (establishing population immunity with or without a vaccine) [28]. China, Singapore, and South Korea have demonstrated an example of suppression strategy [28-34], whereas India [35] and Indonesia [36] have been employing a mitigation strategy. Complete suppression is the ideal strategy in cancer care setting, though the potential socio-economic impact of closing down the society have led countries to employ a mitigation approach over suppression strategies.

Strict social-distancing strategies have led to psychological issues in cancer patients due to the uncertainty of treatment continuation. As leading cancer centers in Asia, participating NCCs in our study provide care to cancer patients throughout the countries and serve as main referral cancer hospital in the region [37]. During the pandemic, access to healthcare is difficult in the current restrictive mobilization state and travel limitation [35]. Furthermore, many patients have been fearful of exposing themselves to the risk of infection and have been more reluctant to present to healthcare services. This situation affects the mental health of the patients and their families in addition to anxiety caused by cancer diagnosis and treatment [37]. The ANCCA members and participating countries have implemented impactful initiatives including travel and vehicle arrangement, employing telemedicine to provide psycho-oncology support, cancer education, nutrition support, and video recording for home-exercise. Automated medication refill and delivery have been also provided to ensure treatment continuity (Table 4). As supported from the literature, communication using digital technology can be adopted as a key strategy to continue delivery of cancer care while protecting vulnerable oncology patients and health care workers [38-39]. Telemedicine is also tool to empower patients and caregivers, therefore alleviate their social burden and improve quality of life [37].

The COVID-19 pandemic is rapidly transforming the medical care system and the use of industry 4.0 technologies has the potential to fulfil customised requirements during the crisis [40]. Several implementations such as telemedicine, utilization of travel databases for adequate screening, as well as virtual meetings admittedly are effective approaches to avoid potential risk of COVID-19 exposure. Going forward, further application of technologies, for instance digital imaging, remote medication supply, the use of machine learning and artificial intelligence for autonomous robot for examination, and the use of virtual reality environment for training and education purposes are transformational windows of opportunity for safer oncology care and training delivery [40]. Virtual care delivery should be appropriately documented to facilitate billing [41]. National health coverage and commercial medical insurance should reconsider to revise their payment policy and provide reimbursement for telemedicine activities in response to pandemic [42]. Currently, telemedicine is more of a use to follow up cases and is not adequate for newly diagnosed of cancer or patients under evaluation. There is still a need of face-to-face consultation for optimal evaluation of new patients. Delaying or postponing cancer treatment due presumed increased risk of infection with COVID-19 is a matter of debate and dilemma [37].

Several studies which demonstrated that cancer patients are more vulnerable to COVID-19 complications have encouraged physicians to withhold or postpone cancer treatment during the epidemic [43-47]. The NCCs have been applying strict social distancing measures that aim to decrease hospital visits and elective procedure. Furthermore, cancer control measures have been temporarily put on hold as NCCs' effort to minimize potential exposure of cancer patients to SARS-CoV-2. Our study showed that cancer control activities, in particular cancer screening and prevention have been impacted in varying degrees. Cancer screening has also been suspended, similarly to several countries in Europe [48], UK [49], US [50-51] following a call from the government to prioritize on coronavirus-related treatments. Halting cancer screening procedures will lead to more advanced stage at diagnosis, and in the future, higher economic burden of a delayed diagnosis of cancer will be loaded on public health economy [52-54]. The NCCs need to prepare for the expected increase of patients when government

decide to loosen the social distancing measure. Huge workload of patient influx in the case of imaging diagnostic on NCC Vietnam is an example of future burden due to delayed diagnosis and cancer treatment that led to risk of exhausted health system.

In the clinical perspective, the paucity of solid evidence on the benefit of treatment modification or interruption should led to careful decision by oncologists and individualized for every patient [25]. Recent studies by Kuderer et al. [55] and Lee et al. [56] argue that treatment delays would significantly cause more harm to cancer patients [52]. In both studies, risk of death of cancer patients who had confirmed coronavirus infection was significantly associated with age, male sex, former smokers, associated comorbidities, active cancer and poor performance score; but not with administration of immunotherapy, chemotherapy, radiation therapy or targeted therapy within 4 weeks of detection of SARS-CoV-2. These evidences clearly urge the need to facilitate the cancer continuum and government decision to re-open the society.

Cancer research and clinical trials

The pandemic has affected clinical care in a broad range of settings, disrupting all aspects of clinical care, including cancer clinical trials. Numerous challenges with conducting clinical trials highlight opportunities to be evaluated and applied as proposed in the US [57] and also in the Asian region. The experience of the nine centers (60%) actively conducting clinical trials provides additional insight on the dramatic impact of the pandemic in Asia, particularly, on patient recruitment and patients' visits for sponsored clinical trials, while investigator-initiated clinical trials were less impacted. Going forward, the restart of clinical studies, as well as the implementation of COVID-19 related clinical trials are likely to create a significant delay and financial burden on the conduct of clinical trials. A new norm will have to be applied around the world to catch up with such huge impact. Unnecessary visits, and other activities set in study protocols can be removed after discussion among pharmaceutical companies, healthcare professionals and patients, to minimize the burden on patients while optimizing well balanced clinical trials.

On the other front, epidemiological and registry research on the impact of COVID-19 on cancer care in national cancer institutions will be key to address issues, not only within clinical trials, but to cover the full scope of cancer care.

Way Forward/Preparing for the future

The COVID-19 pandemic is likely to disrupt health system in lasting ways. Estimating the extent and severity of novel disease outbreaks is dependent on aggressiveness, accessibility and availability of specific testing. Although there could be differences in population demographics and access to healthcare, COVID-19 death rates (as shown in Appendix 1) could be more reflective of the true incidence and impact of the current pandemic. The current strategies taken by NCCs are likely to evolve over time, depending on the stage and width of the pandemic. The priorities are to focus on maintaining cancer care delivery while protecting both patients and health care workers from the risk of COVID-19 transmission. With some countries having loosened up the population-level physical distancing measures and movement restrictions (as of 8-July 2020, the time of this writing) and preparing for their "new normal", NCCs in Asia have to continuously monitor and evaluate the effectiveness of their mitigation strategy (Table 7). ANCCA will keep playing the role of a think-tank, gathering brains to share expertise, lessons learned and allow win/win scenarios among all participating cancer centers (Table 7).

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Statement conflict of Interest

No potential conflict of interest was reported by the authors

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RESEARCH ARTICLE

Cancer Patient Satisfaction and Perception of Chemotherapy Services during COVID-19 Pandemic in Central Java, Indonesia

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Abstract

Background: The COVID-19 pandemic affects all healthcare services, including cancer care. Consequently, our institution implemented several changes in accordance with the National guidelines for managing COVID-19 transmission. However, the patients' perception of such changes is unknown. The objective of this study is to explore the knowledge of cancer patients on COVID-19, their perceptions towards the changes in oncology service, and to identify key elements that contribute to their level of anxiety or comfort. **Methods:** Written questionnaires were given out to cancer patients indicated or undergoing chemotherapy between 23rd June and 3rd July 2020 in a tertiary referral hospital. Data collection was performed 75 days after the implementation of hospital and oncology services changes in response to COVID-19. **Results:** A total of 221 cancer patients participated in this study. The majority of patients possess adequate knowledge and practice appropriate preventive actions. They expressed a positive attitude towards the changes in hospital policies and contented with the consistency of chemotherapy services. The television and internet (social media, communication apps) were the main sources of information for the patient. **Conclusion:** Our institution managed to maintain the consistency of chemotherapy services, despite the implementation of several changes in hospital and treatment policies. With adequate education, patients can remain content and express a positive attitude towards the changes in their treatment experience. Both health care personnel and policymakers should consistently be updated with the continuous surge of publications regarding COVID-19 and adjust their decisions with the best evidence-based practice.

Keywords: oncology- awareness- knowledge- coronavirus- health care

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Introduction

The Indonesian authority declared the first confirmed case of coronavirus disease 2019 (COVID-19) positive patient on 2nd March 2020, a month after the WHO declared the COVID-19 outbreak a public health emergency [1-2]. By Mid July, 80.094 Indonesians were infected with a mortality rate of 4.74% [3]. This highly infectious disease has impacted all aspects of daily life and healthcare services, including cancer care. The delivery of cancer care during the pandemic poses immense challenges, considering the competing risks of mortality related to cancer or the infection of complications related to the SARS-CoV-2 [4]. Early shortage of personal protective equipment (PPE), limited isolation facilities, and lack of testing further complicate the matter. The primary preventive measures to reduce the progression of the disease have been self-isolation, social distancing, hand, and respiratory hygiene. Numerous health officials and expert groups published a multitude of guides on how to care for cancer patients affected by COVID-19 including general precautionary measures to reduce virus transmission [5-10]. Consequently, our institution implemented several changes in accordance with the guidelines to reduce COVID-19 transmission and better allocate limited medical resources. However, the patients' perception of such changes is unknown. The COVID-19 pandemic is affecting global mental health creating anxiety, depression, insomnia, denial, anger, and fear [11]. Cancer patients in particular may experience

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greater psychological stress because of postponed treatment and isolation on top of their inherent disease. Considering the novelty of this disease, there is a paucity of information and experience of cancer management during the pandemic. The objective of this study is to explore cancer patients' perception of oncology service amid the pandemic and to identify key elements that contribute to their level of anxiety or comfort. Obtaining such information may aid policymakers in decision-making to create strategies for ensuring better cancer care during the outbreak.

Materials and Methods

Questionnaire

This qualitative descriptive research aimed to gain information of cancer patient perception on cancer service during the pandemic. Eligible participants were given out a set of questionnaires to be completed during their visit or treatment in our institution. A semi-structured questionnaire was developed by a committee of oncologist, institutional COVID-19 task force and approved by the governing Research Ethics Committee. The questionnaire is comprised of 30 multiple-choice questions divided into 2 parts. The first fifteen questions evaluate the subject's general knowledge of COVID-19 pandemic; awareness on the severity of the outbreak, preventive practices undertaken, and how pandemic affects their daily activities and disease. The rest of the questions explore the subject's experience, level of anxiety, and fear of undergoing chemotherapy. This part also evaluates the quality of healthcare service during the outbreak and allows the respondents to give inputs on what could be implemented to improve it. The questionnaire was created in Indonesian. The English version as seen in Table 2 and Table 3 were translated from Indonesian to English by two different researchers and then reconciled by a third reviewer for the best-corrected version.

Study participants, data collection and analysis

Participants included for this study were all cancer patients indicated for chemotherapy (prior, undergoing, or post) in Dr. Kariadi General Hospital, Semarang, Indonesia. Patients who refused to participate or considered to be clinically unfit were excluded. Two researchers unaffiliated with our institution performed data collection within 22nd June 2020 until 3rd July 2020; 75 days after the implementation of hospital and treatment policy changes on 9th April 2020. Using the convenience-sampling method, all subjects were recruited while waiting in the outpatient oncology clinic or undergoing chemotherapy in the ward. Participant's confidentiality was ensured and that their response will not in any way affect the chemotherapy service. Every subject was given an unlimited amount of time to complete the questionnaire that was collected within the same day.

A family member or the researcher was allowed to assist participants in filling the form. Uncompleted questionnaires were excluded from the analysis. Ethical approval was granted by the hospital Ethics Committee (No.543/EC/KEPK-RSDK.2020). Data were tabulated and analyzed using Microsoft Excel for Mac 2011 Version 14.4.1 (Microsoft Corporation, Washington, United States). Continuous variables are presented as total number (n) and percentage (%) unless stated otherwise.

Results

A significant majority of the 221 participants in this study were Javanese females diagnosed with breast cancer with below than average level of income. The patients' demographic data are presented in Table 1. The coronavirus outbreak disrupted the daily activities of almost all patients

Table 1. Patient Demographics

Patient demographics	n	%
Total	221	100,0
Female	183	82,8
Age (years old)[a]	49.2; 50; 20-82	
No. household member[a]	3.8; 4; 1-10	
Married	201	91,0
Ethnicity		
Javanese	214	96,8
Chinese	3	1,4
Betawi	1	0,5
Dayak	1	0,5
Malay	1	0,5
Level of education		
No formal education	12	5,4
Elementary	50	22,6
Middle	47	21,3
High	61	27,6
College and above	51	23,1
Level of monthy income[b]		
Below average	144	65,2
Average	72	32,6
Above average	5	2,3
Cancer diagnosis		
Breast	131	59,3
Gynecologic	15	6,8
Hematology	7	3,2
Colorectal	8	3,6
Head and Neck	31	14,0
Urology	5	2,3
Lung	5	2,3
Skin	1	0,5
Lymphoma	14	6,3
Sarcoma	4	1,8
No. of chemotherapy		
<5	81	36,7
5 to 20	125	56,6
>20	15	6,8

[a]Data presented as mean, median, and minimum-maximum respectively
[b]Below average: <3 million Indonesian Rupiah (IDR), average 3-15 million IDR, above average >15 million IDR

Table 2. General Knowledge and Awareness of COVID-19

Questions	Answer	n	%
Q1. Are you worried about being infected by the Corona virus?	Very worried	65	29,4
	Worried	106	48,0
	Not Worry	50	22,6
Q2. Are you or have you been infected with Corona virus?	Yes	0	0,0
	No	179	81,0
	Do not know	42	19,0
Q3. If you answer Yes or No above, have you undergone a Corona examination?	Yes	16	7,2
	No	205	92,8
Q4. Is your daily activities disrupted since the pandemic began?	Very	57	25,8
	Yes	85	38,5
	A little	77	34,8
	Not at all	2	0,9
Q5. Have you been staying at home and avoid social events since the outbreak?	Yes	210	95,0
	No	11	5,0
Q6. Have you been keeping a safe distance of two meters from other people?	Yes	215	97,3
	No	6	2,7
Q7. Did you wash your hands more often since the outbreak?	Yes	219	99,1
	No	2	0,9
Q8. Have you been wearing a mask when your leave the house or meet other people?	Yes	219	99,1
	No	2	0,9
Q9. In your opinion, should people cancel and avoid social events during the outbreak?	Yes	198	89,6
	No	23	10,4
Q10. In your opinion, should people avoid shaking hands during the outbreak?	Yes	207	93,7
	No	14	6,3
Q11. In your opinion, should all non-essential stores (other than supermarkets, pharmacies, post offices, gas stations, etc.) be closed during the pandemic?	Yes	69	31,2
	No	152	68,8
Q12. In your opinion, should there be a curfew (except for grocery shopping, work, medical treatment)?	Yes	169	76,5
	No	52	23,5
Q13. Can the Corona virus infection make your cancer worse?	Yes	97	43,9
	No	124	56,1
Q14. Where did you get information about COVID-19?	Radio	1	0,5
	Television	157	71,0
	Internet	56	25,3
	Other	7	3,2
Q15. What are your esStimates of the number of Indonesians infection with Corona virus at this time?	<100	5	2,3
	100-1.000	36	16,3
	5000	29	13,1
	5000-10.000	48	21,7
	> 10.000	103	46,6

(219 out of 221, 99.1%), significantly affecting a quarter of them. A considerable number of patients claimed to be not worried of being infected (50 out of 221, 22.6%), although virtually all of them have adopted the basic preventive measures: self-isolation (210 out of 221, 95%), social distancing (215 out of 221, 97.3%), hand (219 out of 221, 99.1%) and respiratory hygiene (219 out of 221, 99.1%). Most agreed that non-essential stores should not be closed during the pandemic (152 out of 221, 68.8%) with a curfew in place (169 out of 221, 76.5%). The patients are divided approximately in half between those believed coronavirus infections can make their cancer worse (97 out of 221, 43.9%) and those who do not (124 out of 221, 56.1%). The major sources of information were television (157 out of 221, 71%) and the internet (56 out of 221, 25.3%) that include mobile communication and social media applications. Evaluation of subjects' knowledge and awareness of the pandemic is presented in Table 2. Eight-one patients admitted to be afraid of being infected by the coronavirus while undergoing chemotherapy, with a minority of them considered stopping chemotherapy or coming to the oncology clinic altogether. Most patients can resume their treatment with no difficulty, while the rest claimed to be affected by harder access to the hospital (42 out of 221, 19%), treatment postponement (5 out of 221, 2.3%), longer queue (11 out of 221, 5.0%), and limited

Table 3. Patient Satisfaction and Perception of Chemotherapy Services during COVID-19 Pandemic

Questions	Answer	n	%
Q16. Are you afraid of being infected with Corona virus while undergoing chemotherapy at the hospital?	Very afraid	90	40,7
	Somewhat afraid	89	40,3
	Not afraid	42	19,0
Q17. Have you thought of stopping or delaying chemotherapy during the outbreak?	Yes	30	13,6
	No	191	86,4
Q18. Have you thought of stopping going to the clinic routinely during the outbreak?	Yes	28	12,7
	No	193	87,3
Q19. Have you ever faced difficulty in getting chemotherapy during the outbreak? If yes, what was the cause?	No difficulty	154	69,7
	Access to hospital	42	19,0
	Treatment postponement	5	2,3
	Longer treatment queue	11	5,0
	Limited hospital workers	2	0,9
	Other	7	3,2
Q20. Did you experience any changes in the chemotherapy service during the outbreak?	Yes	80	36,2
	No	141	63,8
Q21. In your opinion, is the hospital's safety measures and policy in dealing with the Corona virus outbreak adequate?	Not adequate at all	1	0,5
	Not adequate	8	3,6
	Adequate	106	48,0
	More than adequate	105	47,5
Q22. In your opinion, are the measures and personal protective equipment used by hospital workers adequate to prevent Corona virus transmission within the hospital?	Not adequate at all	2	0,9
	Not adequate	4	1,8
	Adequate	108	48,9
	More than adequate	107	48,4
Q23. How much do you trust the hospital workers (doctors, nurses, administrators, etc.) in maintaining your safety?	Not at all	1	0,5
	A little	3	1,4
	Neutral	31	14,0
	Trust	11	5,0
	Very trusting	175	79,2
Q24. Is there a change in the health care service quality during the outbreak?	Got very bad	0	0,0
	A little worse	7	3,2
	The same	113	51,1
	Better	80	36,2
	Become much better	21	9,5
Q25. Were you educated about the Corona virus outbreak by the chemotherapy unit workers (doctors, nurses, ward officers)?	Not at all	76	34,4
	A little	57	25,8
	Yes	68	30,8
	A lot	20	9,0
Q26. Where did you get most information about the Corona virus and its relationship to your disease?	Doctor	27	12,2
	Nurse	14	6,3
	Administrators	3	1,4
	Hospital announcements (television, brochures)	113	51,1
	Other	64	29,0
Q27. What about the quality of chemotherapy services you received during the outbreak?	Got very bad	0	0,0
	A little worse	1	0,5
	The same	124	56,1
	Better	87	39,4
	Become much better	9	4,1

Continued Table 3.

Questions	Answer	n	%
Q28. What do you think can best improve the quality of chemotherapy services?	More PPE worn by hospital workers	116	52,5
	More PPE provided	30	13,6
	More education from hospital workers	40	18,1
	Speed up chemotherapy program	30	13,6
	Stopping or delaying chemotherapy	1	0,5
	Other	4	1,8
Q29. Are you afraid or worried about going to the oncology clinic during the outbreak?	Yes, very	56	25,3
	A little	76	34,4
	Not afraid/ worried	89	40,3
Q30. In your opinion, what is the most useful way to reduce the level of anxiety or fear when undergoing chemotherapy during the outbreak?	Wearing PPE	124	56,1
	PPE worn by hospital workers	47	21,3
	Education and communication with hospital workers	27	12,2
	Speed up chemotherapy program	21	9,5
	Stopping or delaying chemotherapy	1	0,5
	Other	1	0,5

hospital workers (2 out of 221, 0.9%).

The majority of patients trusted the new hospital policies (211 out of 221, 95.5%), PPE (215 out of 221, 97.3%) and workers (217 out of 221, 98.2%) for being able to maintain their safety and deliver safe treatment. More than half of the respondents claimed that the quality of both general health care services and chemotherapy remained consistent or even better during the outbreak. Most respondents agreed that more PPE worn by the hospital workers and themselves may improve the quality of chemotherapy service and lower their level of anxiety. Patient perception and satisfaction of oncologic service are presented in Table 3.

Discussion

The COVID-19 pandemic is an ongoing International concern that created unprecedented media attention and coverage. Never before a disease entity created such interests from the global population across all socioeconomic backgrounds. In Indonesia, the COVID-19 received substantial social publications across all platforms, chiefly the television, internet (including social media, mobile communication app) newspaper (paper and electronic), radio, and mural advertising educating the people with the basic knowledge of coronavirus epidemiology, virology, and prevention [12]. The mass media proved to be a very efficient way of information transfer, as supported by the findings of this survey. Almost all patients (213 out of 221, 96.4%) obtained information about COVID-19 from either the television or the internet. They claimed to be well-informed and successfully practiced social isolation, physical distancing, improved hand, and respiratory hygiene. On the other hand, less than 40% of patients reported being adequately educated by the chemotherapy unit workers (doctors, nurses, ward officers). In this extraordinary circumstance, the mass media is undoubtedly faster and more efficient compared to the direct doctor-to-patient education system.

However, the deficiency in doctor-to-patient education should be addressed considering the media does not broadcast in-depth knowledge such as the relationship between COVID-19, cancer, and chemotherapy.

Only 27 (12.2%) patients in our study claimed to be educated their physicians in regard to this matter. Access and comprehension of advanced medical information are limited to healthcare professionals. Extensive media coverage of the coronavirus outbreak may also be counterproductive by creating exacerbated public fear, panic, and stress [13]. Thus physicians play a major role in patient education by being able to practice evidence-based medicine, filter fallacious information, and control patient apprehension. In short, it is advisable for policymakers to capitalize on effective educational platforms (e.g. hospital televised infomercial, hospital mobile app), without abandoning the physician's pivotal role in direct patient education.

Following the declaration of COVID-19 as a global emergency, the Indonesian Government created the COVID-19 Response Acceleration Task Force (CRATF) in an effort to accelerate the mitigation of coronavirus disease. Coordinated by the Indonesian National Board for Disaster Management, Ministry of Health, National Police and Armed force, the task force published a series of guidelines for all sectors aiming to manage the outbreak [14]. The guideline for health care sector was formulated

Table 4. COVID-19 Patient Categorization and Initial Approach

No	Fever / history of fever	Respiratory symptoms[a]	Transmission region[b]	Close contact with confirmed case	Patient category[c]	Management
1	+	+	+		PUS	CBC, WBCD, CXR, NPS
2	±	±		+	PUS	
3	+	+ (severe)			PUS	Hospital admission (isolation ward), NPS
4	±	±	+		PUM	>60 yo: CBC, WBCD, CXR, NPS
5		+		+	PUM	<60 yo with comorbidities: CBC, WBCD, CXR,NPS <60 yo without comorbidities: NPS
6				+	PWS	NPS
7			+			Education and self isolation

[a]Cough/dyspnea/sore throat/rhinorrhea, [b]person from transmission region as defined by the Indonesian COVID-19 Task Force [3], [c]Since 14 July 2020 the Indonesian COVID-19 patient category system followed the case definitions as defined by the WHO [24]. ± at least one positive; PUS, patient under surveillance; PUM, person under monitoring; PWS, person without symptom; CBC, complete blood count; WBCD, white blood cell differential; CXR, chest x-ray; NPS, 2 consecutive days of nasopharyngeal swabs for RT-PCR assays.

from collective information from several of the Nation's medical specialist associations [15]. Hospitals are advised to follow this guideline, however, it can be adjusted based on the available human resources and medical facilities of each region. As a tertiary referral hospital, our oncology center adhered to the local hospital guideline that is in concordance with the COVID-19 guideline published by the National Task Force.

Online reservation for clinical follow-up or chemotherapy was made mandatory since the pandemic. All patients were instructed to come at most 15 minutes before the designated time and instructed to directly go home after they are done. Before entering the building, all patients were screened by trained personnel using the COVID-19 early warning score (EWS) screening tool [16] and classified into one of the four patient categories based on their relation with COVID-19: person without symptom (PWS), person under monitoring (PUM), patient under surveillance (PUS), and confirmed case. Case definitions and initial approaches are summarized in Table 4.

Only those who are not suspected of COVID-19 were allowed inside to continue their treatment otherwise, the patient is directed to a dedicated COVID-19 management area within the hospital complex. All hospital staffs within the premise continuously enforce facemask usage and physical distancing. Such precautionary measures would have been a major inconvenience for patients in the pre-COVID era by creating longer queues and discomfort. Anxiety is a common problem in cancer patients and will negatively impact their quality of life, treatment satisfaction, and outcome [17]. The fear of contracting coronavirus aggravates this problem, as shown in our study that 81% of the patients were afraid of being infected while undergoing chemotherapy. Some of them even thought of stopping chemotherapy (30 out of 221, 13.6%) or coming to the clinic for follow-up altogether (28 out of 221, 12.7%). Although COVID-19 preventive measures are not 100% effective in preventing disease transmission, we think its application is detrimental for patients by creating a "sense of security" reducing their level of anxiety and fear. Almost all respondents trusted the hospital's policy in handling COVID-19 and put confidence in the hospital staff for maintaining their safety. Based on this survey, PPE worn by the healthcare personnel and patient is the major anxiety-reducing factor while undergoing chemotherapy. The level of PPE worn by hospital personnel was deemed adequate by 97.3% of respondents. However interestingly, half of them think that more PPE worn by hospital workers can further improve the quality of service. Our institution was able to maintain the quality of chemotherapy service during the pandemic. About half of the respondents (113 out of 221, 51.1%) think the quality of service remains the same and even improved during the pandemic. Most patients in our study (154 out of 221, 69.7%) were able to resume their chemotherapy normally since the pandemic. Some patients (42 out of 221, 19%) patients had problems coming to the hospital from neighboring cities because of the inter-city travel bans imposed by the government from late April until early June.

The main dilemma for continuing chemotherapy during the crisis is the potential infection of COVID-19. Limited data from the Chinese population suggest cancer patients who contracted COVID-19 suffered from higher rates of severe events and mortality compared to their counterparts [18-19]. However, a current systematic review does not support interruption of chemotherapy or immunotherapy for cancer patients and does not recommend withholding anticancer therapy for those who do not have COVID-19 [20]. One prospective cohort study suggests that mortality from COVID-19 in cancer patients is more driven by age, gender, and comorbidities [21]. Solid data is lacking to draw any conclusion in the potential harm from interrupting chemotherapy versus the benefits of possibly preventing COVID-19 infection. In this light, many clinical resources have recently been published guidelines for health care professionals on the proper recommendations to deliver safe and effective oncologic services.

Major guidelines generally advise the approach should be individualized based on the patient's level of priority. The American Society of Clinical Oncology (ASCO) advised clinical decision to be based on cancer curability, risk of recurrence with treatment modification

or interruption, the number of cycles already completed, and patient's tolerance to treatment. Chemotherapy recommendations set forth by ASCO include stopping chemotherapy as an option for those in deep remission receiving maintenance therapy or in cases where the clinical benefit of adjuvant chemotherapy is expected to be small, start oral chemotherapy or home infusion, alter treatment schedule for fewer visits, and to be selective in using drugs that inhibit B cells such as anti-CD20 monoclonal antibodies [9]. The European Society for Medical Oncology (ESMO) similarly recommends classifying and treating cancer patients according to their level of priority. The proposed cancer patient prioritizations proposed by the ESMO-Magnitude of Clinical Benefits (ESMO-MCBS) are [1] high priority patients who are in an immediate life-threatening, a clinically unstable disease where treatment is ideally not delayed, [2] medium priority patients in a non-critical situation that treatment delay for more than 6 weeks may adversely affect the overall clinical outcome, [3] low priority patients in a condition that is stable enough that treatment can be delayed for the duration of COVID-19 pandemic [6].

A national guideline published by The Indonesian Society of Surgical Oncology (ISSO) is in accord with several International guidelines (10). For example prioritization, treatment, and triage of breast cancer patients is consistent with the recommendations made by the American Society of Breast Surgeons (ASBrS) [22]. Thyroid cancer management is based on the British Association of Endocrine and Thyroid Surgeons (BAETS) statement [23]. Management of melanoma and sarcoma adhered to the guidelines published by ESMO [6]. In our institution, the decision whether or not to postpone cancer treatment were made on a patient-by-patient basis by the oncologists' clinical judgment. Current local hospital guideline does not dictate specifically in regards to this matter. To which practice guidelines each oncologist follow was not recorded and is beyond the scope of this study. Only 5 (2.3%) patients experienced treatment postponement during the course of this survey that suggests treatment interruption is uncommon. The oncology working groups to meet and reach a conclusion on which guideline that they are going to follow to maintain service quality.

The inherent limitation of this study is the small size convenience sampling that is not translatable to the general population. Since the majority of cancer patients in our hospital were breast, head, and neck cancers, there may be selection bias caused by venue selection to distribute the questionnaires. Since data collection was performed in a cross-sectional fashion the causal relationship between the variables cannot be made.

In conclusion, the COVID-19 pandemic significantly alters all aspects of life, including health care services. Changes in hospital treatment policies in an attempt to manage disease transmission may inadvertently impose a greater level of anxiety and unnecessary treatment interruption for cancer patients. The effectiveness of the media in spreading general knowledge about of COVID-19 is undeniable. However, information sharing through this platform may backfire by being misinterpreted and creates exaggerated fear. Findings from this study suggest that the majority of Indonesian cancer patients in Central Java possess adequate knowledge and successfully practiced appropriate preventive measures towards the COVID-19 pandemic. They expressed a positive attitude towards the changes in hospital policies and were generally happy with the consistency of chemotherapy services during the pandemic. So far, alterations in the treatment program were individualized for each cancer type by the oncologists in accordance with their respective specialist association guidelines. Definitive data on the risks and benefits of altering chemotherapy for cancer patients during COVID-19 remains to be elucidated and will require longer prospective observations from cases all around the world.

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RESEARCH ARTICLE

Patterns of Care of Gallbladder Cancer During the COVID-19 Pandemic: An Experience of Tertiary Care Centre at Patna, India

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Abstract

Introduction: The novel coronavirus disease 2019 (COVID-19), is caused by the severe acute respiratory syndrome cronavirus 2 (SARS-CoV2). The management of cancer patients is very challenging during the COVID-19 pandemic. Cancer itself as well as anticancer treatment leads to compromised immunity of patients with increased risk of infection. This is turn leads to increased hospital visits. It forms a vicious cycle that increases the risk of COVID-19 susceptibility to cancer patients. Patients on anticancer treatment alongwith COVID-19 infection have higher risk of morbidity and mortality. **Aim:** To compare the epidemiological characteristics and management decisions in gallbladder cancer patients during COVID-19 pandemic. **Methods:** This retrospective study was conducted at All India Institute of Medical Sciences (AIIMS), Patna. Patients were divided into two group pre-COVID (patients attending radiotherapy department from December 2019 to February 2020) and established-COVID group patients (patients attending radiotherapy department from March 2020 to May 2020) with histopathological confirmed diagnosis of gallbladder cancer. **Results:** Histopathological confirmed cases of gallbladder cancer (n=85) were analyzed, 56 patients from pre-COVID timeline and 29 patients from established-COVID timeline were selected. During the pre-COVID timeline, 55.4% of the patients directly visited the radiotherapy department while, 24.1% patients directly attended the radiotherapy department during the established-COVID time. This reduction of number of patients at radiotherapy department was statistically significant ($p = 0.006$). There was statistically significant reduction ($p = 0.014$) in number of patients attending from rural areas during established-COVID time. Chemotherapy regimen used during pre-COVID and established-COVID timeline was significantly ($p < 0.001$) different. **Conclusion:** Cancer patient management during COVID-19 pandemic is an important issue. Chemotherapy increases the risk of COVID-19 infection by reducing the immunity. Single agent oral capecitabine is a good option for patients of gallbladder cancer in the adjuvant or palliative settings with less toxicity and requiring less hospital visits compared to intravenous chemotherapy.

Keywords: COVID-19- gallbladder cancer and COVID pandemic- India

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Introduction

The novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome cronavirus 2 (SARS-CoV2). COVID-19 was declared as a pandemic on 11th March 2020 by the World Health Organization (WHO) [1-2]. The COVID-19 pandemic is on the rise and has reached most parts of the world. The increase in number of cases had a significant impact on the health care resources. The resources of health care management are diverted towards prevention and management of COVID-19 cases in terms of intensive care units, ventilators, health care workers and others resources [3]. All over the world, "lockdown" or "social distancing" has been considered the most effective method to control the outbreak of COVID-19 [4]. Due to the high infectivity

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rate and rapid increase in number of cases affected with COVID-19, most of health care institutes or hospitals have reduced or stopped the elective interventions. Cancer management is always a multidisciplinary approach, hence suggested to be well planned with discussion regarding type of intervention and expected outcome. Cancer treatment is considered as nonemergency [5], however patients cannot persistently wait to start therapy. The National Cancer Registry Programme of India showed 14.6 cancer cases per lakh population [6]. Cancer care is resource consuming and requires social and moral support for the patients. In the current COVID-19 pandemic there is no evidence based guidelines for the management of cancer patients. Gallbladder cancer is associated with advanced stage at presentation and poor outcome in view of its nonspecific symptoms. It is also highly prevalent in the Gangetic plains of India [7]. Treatment consists of surgery followed by adjuvant chemotherapy or radiation for early operable cases [8]. However, most of our patients present late where only palliative chemotherapy or best supportive care can be offered. There are concerns regarding the administration of systemic chemotherapeutic agents in cancer patients during this pandemic. The systemic chemotherapeutic agents make the patients susceptible to COVID-19 infection due to immunosuppression [9]. Patients with cancer who have COVID-19 infection have a higher risk of mortality and complications [10]. In the absence of evidence-based guidelines, there is a dilemma about whether to administer systemic chemotherapy. We conducted retrospective analysis to assess the epidemiology and patterns of care in gallbladder cancer patients during the pandemic.

Materials and Methods

General methodology

A retrospective analysis was performed in the department of radiotherapy at All India Institute of Medical Sciences (AIIMS), Patna, a tertiary care center in Bihar, India. The data were obtained from departmental records. From 1st December 2019 to 31st May 2020.

Patient selection

Patients histopathologically diagnosed with gallbladder cancer attending radiotherapy department from December 2019 to May 2020, were selected for analysis. The patients were divided into two-group pre-COVID and established-COVID There was no clear demarcation between these two groups. First case of COVID-19 was confirmed in India on 30 January 2020. By the end of February 2020, only two confirmed cases of COVID-19 were seen in India. Therefore, patients attending radiotherapy department from December 2019 to February 2020 were included in pre-COVID group and form March 2020 to May 2020 included in established-COVID group. First case of COVID-19 was confirmed, in Bihar from Munger district on 22 March 2020. There was steady rise of COVID-19 cases since then in Bihar. The adjuvant or palliative chemotherapy commonly advised at AIIMS, Patna for gallbladder cancer includes injection Gemcitabine 1000 mg/m^2 day1, 8 and Oxaliplatin 80 mg/m^2 day 1, 8 with 3 weekly cycles (Gem/Ox) regimen. Those patients started on Gem/Ox regimen during pre-COVID time were considered for same Gem/Ox regimen during the established-COVID time but the day 8 was omitted to reduce the number of hospital visits. Patient diagnosed with gallbladder cancer during the established-COVID, having an indication of adjuvant or palliative chemotherapy were considered for any of the following chemotherapy regimen: Gem/Ox or single agent oral capecitabine 1000 mg/m^2 orally day 1 to day 14, three weekly (Cap) regimen or injection gemcitabine 1000 mg/m^2 day 1, 8 and tablet capecitabine 825 mg/m^2 orally day 1 to day 14, three weekly cycle (Gem/Cap) regimen. Again, to reduce the hospital visit and chemotherapy related toxicities day 8 of Gem/Ox or Gem/Cap regimen was omitted. Patients whose general condition did not permit were given best supportive care.

Treatment of any kind to the patient provides psychological benefit to them whatever is the stage of the disease. Best supportive care includes the adequate pain relief with analgesics, management of toxicities, and the care of nutritional needs. While providing best supportive care to patients the caregivers or attendants were sensitized, regarding less hospital visit during the established-COVID pandemic and encouraged for the use of telemedicine facility of AIIMS, Patna.

Data collection

Retrospectively data was retrieved from recorded files from the department of radiotherapy. Data was collected with respect to age, gender, referred cases from other department or first visit, address (district), distance from Patna, rural or urban residence, Eastern Cooperative Oncology Group Performance Status (ECOG PS), stage, surgery, and management decision.

Data analysis

The data were analyzed using the Statistical Package for the Social Science (SPSS version 25, IBM Corp). Two sided Chi-square test with $p = 0.05$ or less was considered statistically significant.

Results

The COVID time

Eighty five (n=85) patients of histopathologically confirmed gallbladder cancer were analyzed who attended the radiotherapy department of AIIMS, Patna from December 2019 to May 2020. The number of patients in pre-COVID and established-COVID periods were 56 and 29 respectively.

Epidemiological characteristics

Patients attending radiotherapy department were divided into two groups, new cases who directly visit radiotherapy outpatient for consultation and patients who attends radiotherapy department with referral from other departments. During the pre-COVID timeline, 55.4% of the patients directly visited the radiotherapy department while

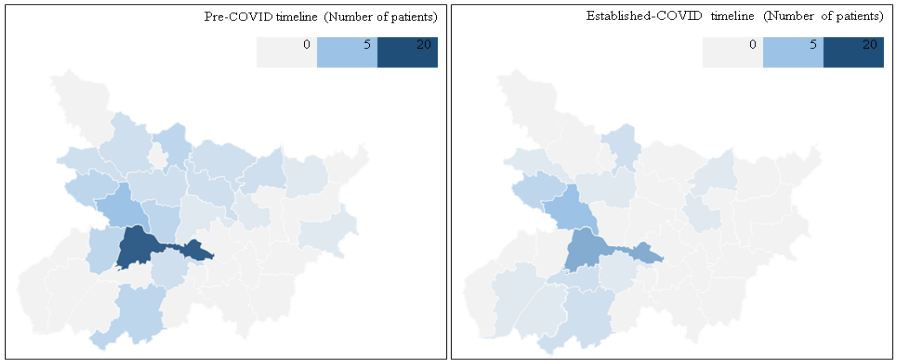
Table 1. Epidemiological and Clinical Characteristics of the Patients

		Peri-COVID time				
		Pre-COVID		Established-COVID		p - value
		N=56	Table N (%)	N=29	Table N (%)	
Type of case	New	31	55.40	7	24.10	0.006
	Referral	25	44.60	22	75.90	
Age group	Upto 30 years	0	0.00	2	6.90	0.097
	30 - 40 years	10	17.90	1	3.40	
	41 -50 years	17	30.40	11	37.90	
	51 - 60 years	13	23.20	6	20.70	
	61 - 70 years	13	23.20	9	31.00	
	> 70 years	3	5.40	0	0.00	
Gender	Male	24	42.90	6	20.70	0.043
	Female	32	57.10	23	79.30	
Distance group	< 50 km	21	37.50	10	34.50	0.891
	51 - 100 km	13	23.20	9	31.00	
	101 - 150 km	16	28.60	8	27.60	
	151 - 200 km	5	8.90	2	6.90	
	201 - 250 km	0	0.00	0	0.00	
	> 251 km	1	1.80	0	0.00	
Rural/urban	Rural	29	51.80	7	24.10	0.014
	Urban	27	48.20	22	75.90	
ECOG	ECOG 0	7	12.50	0	0.00	0.288
	ECOG 1	6	10.70	3	10.30	
	ECOG 2	16	28.60	9	31.00	
	ECOG 3	17	30.40	13	44.80	
	ECOG 4	10	17.90	4	13.80	
Jaundice	Yes	20	35.70	7	24.10	0.277
	No	36	64.30	22	75.90	
Stage	Stage 1	0	0.00	0	0.00	0.427
	Stage 2	2	3.60	3	10.30	
	Stage 3	10	17.90	4	13.80	
	Stage 4	44	78.60	22	75.90	
Metastasis	Yes	44	78.60	22	75.90	0.776
	No	12	21.40	7	24.10	
Surgery	Yes	12	21.40	6	20.70	0.937
	No	44	78.60	23	79.30	
Management	Adjuvant	12	21.40	6	20.70	0.786
	Palliative	34	60.70	16	55.20	
	Best supportive care	10	17.90	7	24.10	
Regimen	No chemotherapy	10	17.90	7	24.10	< 0.001
	Capecitabine	0	0.00	11	37.90	
	Gem / Ox	46	82.10	5	17.20	
	Gem / CAP	0	0.00	6	20.70	

ECOG- Eastern Cooperative Oncology Group; CAP- capecitabine; Gem- gemcitabine; Ox- Oxaliplatin; km- kilometer; COVID- novel coronavirus disease

44.6% patients were referred from other departments. During the established-COVID time, 24.1% patients directly attended the radiotherapy department and 75.9% patients were referred from other departments. The change in patients referral was statistically significant (p = 0.006).

The distribution of the patient was analyzed according to the district from where they belong during pre-COVID and established-COVID time and is shown in Figure 1a and 1b. The male and female patients were 42.9% and 44.6% respectively in pre-COVID timeline. The male



1a 1b

Figure 1. 1a, Distribution of Patients According to Residential Districts of Bihar During pre-COVID Timeline. 1b, Distribution of Patients According to Residential Districts of Bihar During Established-COVID Timeline.

and female patients were 20.7% and 79.3% respectively in established-COVID timeline. The gender-wise distribution of patient were differing while comparing them with pre-COVID and established-COVID, these differences were statistically significant (p = 0.043). The median age of patient was 53 years and the most common age group of patients was 41-50 years in both pre and established-COVID. The distribution of patient according to age group shown in Figure 2. During pre-COVID time 35.7% of patients presented with jaundice and during established-COVID 24.1% presented with jaundice. The median value of CA19.9 was 327 U/ml and 254 U/ml in pre-COVID and established-COVID time respectively. The patients from rural area were 51.8% and 24.1% in pre-COVID and established-COVID timeline respectively and the difference was statistically significant (p = 0.014). Distribution of patient according to the area of residence depicted in Figure 3. ECOG PS at presentation was ECOG 3 in both pre-COVID (30.4%) and established-COVID (44.8%). Stage 4 was the most common stage at presentation. 78.6% and 75.9% of patients presented with metastasis during pre and established-COVID respectively. In pre-COVID timeline adjuvant chemotherapy, palliative chemotherapy, and best supportive care was considered in 21.4%, 60.7%, and 17.9% respectively. During established-COVID timeline adjuvant chemotherapy, palliative chemotherapy, and best supportive care was considered in 20.7%, 55.2%, and 24.1% respectively. Patterns of management was not statistically significant (p = 0.786). In pre-COVID timeline best supportive care was advised in 17.9% of patients, 21.7% adjuvant intravenous chemotherapy and 60.4% palliative chemotherapy while 24.1% received best supportive care, 37.9% adjuvant or palliative oral chemotherapy, and 37.9% received adjuvant or palliative intravenous chemotherapy in established-COVID. This difference in regimen of chemotherapy was statistically significant (p < 0.001). The baseline epidemiological characteristics are shown in Table 1.

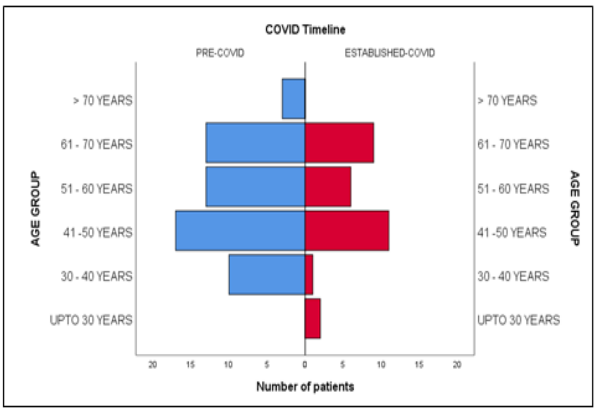


Figure 2. Distribution of Patients During Pre and Established COVID According to Age Group

Patient care

Treatment intent

Out of 56 patients in pre-COVID group, 12 (21.4%) patients underwent surgical intervention and were planned for adjuvant treatment in form of systemic chemotherapy alone or chemotherapy and radiotherapy. Palliative systemic chemotherapy Gem/Ox was considered in 34 (60.7%) patients. Best supportive care advised in 10 (17.9%) patients. In established-COVID group, out of 29 patients 6 (20.7%) patients underwent surgical intervention and considered for adjuvant chemotherapy (Gem/Ox or Gem/Cap or Cap alone). Only one patient was enrolled for neoadjuvant chemotherapy (Gem/Ox) followed by surgical assessment. 16 (55.2%) patients out of 22 who presented with metastatic disease were considered for palliative chemotherapy and 7 (24.1%) advised for best supportive care. Adjuvant and palliative chemotherapy was advised in 6 (20.7%) and 16 (55.2%) respectively. Best supportive care was considered in 7 (24.1%) patients. To reduce the hospital visit in view of COVID-19 pandemic day 8 of the regimens were omitted.

Chemotherapy

Adjuvant and palliative chemotherapy in pre-COVID group was consisted Gem/Ox, which was considered in 82.1% of patients including adjuvant (21.4%) and palliative (60.7%) intent. In established-COVID group, adjuvant and palliative chemotherapy regimen used were

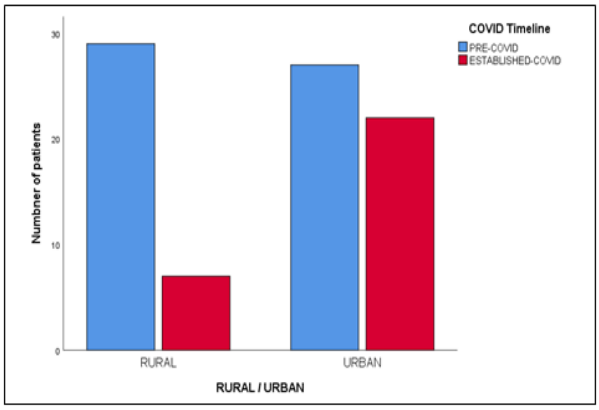


Figure 3. Distribution of Patients During Pre and Established-COVID According to Area of Residence (rural or urban)

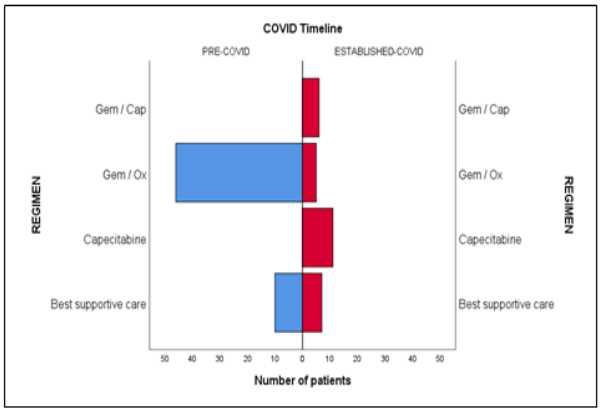


Figure 4. Distribution of Patients During Pre and Established COVID Received Different Types of Chemotherapy Regimens

as Gem/Ox, Gem/Cap, and Cap only. Gem/Ox, Gem/Cap, and Cap was advised in 17.2%, 20.7%, and 37.9% respectively depending on the ECOG PS, stage, and distance from health care facility. Distribution of patients according to chemotherapy regimen advised is depicted in Figure 4. There was statistically significant difference in the selection of chemotherapy regimen during pre-COVID and established-COVID time ($p < 0.001$).

Best supportive care

Best supportive care was advised to the patients according to the stage, ECOG PS, health care access facility, and severity of the symptoms. WHO ladder of pain control was followed for pain management. Adequate pain relief with analgesics, management of toxicities, and the care of nutritional needs were remained the integral part best supportive care. Best supportive care was 17.9% and 24.1% during pre-COVID and established-COVID timeline. This increase in number of patient for best supportive care was not statistically significant ($p = 0.786$).

Discussion

Gallbladder cancer is one of the most common malignancies in this part of the world. The majority of the gallbladder cancer patients presents in an advanced stage with poor prognosis. The medial survival of gallbladder cancer patients is around 6 months [11]. A study by Liang W et al. suggested that cancer patients with COVID-19 infection undergoing treatment have a higher morbidity and mortality [12]. The health care system is already burdened during the COVID-19 pandemic due to resource mobilization towards management of COVID-19 cases. Cancer patients planned for intravenous (IV) systemic chemotherapy are at higher risk of hospital acquired COVID-19 infection due to frequent hospital visits. There is significant reduction in the number of patients attending health care facility during the established-COVID time. In this study, there is 48.21% reduction in the number of gallbladder cancer patients in established-COVID time as compared to pre-COVID time. There was significant reduction in number of patients with gallbladder cancer, especially the patients who directly attended the radiotherapy department in established-COVID timeline. We found that the main proportion of the patients (75.9%) with gallbladder cancer were actually referred from different departments during the established-COVID timeline, while in pre-COVID time the referral cases from other departments were 44.6%. The most common age group at presentation remains same 41 – 50 years. 37.5% of patients were within a range of < 50 kilometer (KM) of distance from AIIMS, Patna in pre-COVID time. In established-COVID time, 34.5% of patients were from distance within < 50 KM. Before the established-COVID time the most of the patients were attending from the rural areas (51.8%) while during the established-COVID time most of the patients attending AIIMS, Patna were from urban areas (75.9%). This may be due to the lockdown started by Government of India on 24th of March 2020 and inadequate access of mode of transport or other resources. In this study, the clinical presentation of patients while comparing the pre-COVID and established-COVID remains similar with respect to jaundice, stage, and surgical resectability. In this study, 30.4% of patients presented with ECOG 3 in pre-COVID time and 44.8% of patients presented with ECOG 3 at established-COVID time. This increase in percentage of patients of gallbladder cancer with poor ECOG may be due to inadequate transportation availability and strict enforcement of lockdown rules. Most of them were planned for palliative single agent capecitabine. The advantage of oral capecitabine is being in terms of ease of administration, less toxic, taken at home in isolated setting, and requiring less hospital visits while comparing to other systemic intravenous chemotherapy. Patt YZ et al. demonstrated the advantage of single agent capecitabine in adjuvant setting over Gem/Ox, but the numbers of patients were very small in their study [13]. Postoperative case of gallbladder cancer that had an indication of adjuvant treatment, adjuvant treatment was advised generally in the form of intravenous systemic chemotherapy with or without adjuvant radiation. During

the pre-COVID time, Gem/Ox was the most commonly advised adjuvant chemotherapy at our institute. During the established-COVID time the patients had an indication of adjuvant chemotherapy were also considered for Gem/Ox, but day 8 chemotherapy was omitted. Single agent oral Capecitabine is also an option for patients requiring adjuvant chemotherapy as per American Society of Clinical Oncology [14]. In this study, 37.9% of patients were advised for single agent capecitabine either as an adjuvant or palliative chemotherapy due to ease of its administration and need of less frequent visit with manageable toxicity during the established-COVID time. BILCAP trial showed the advantage of gemcitabine over observation only in per-protocol analysis [15]. In this study, patients advised for best supportive care were 17.9% and 24.1% during pre-COVID and established-COVID timeline. This increase in number of patient for best supportive care was not statistically significant ($p = 0.786$). Best supportive care included adequate pain relief with analgesics, management of toxicities, optimal nutritional care. To reduce the number of hospital visits telemedicine facility were utilized. Recent publication by Patel A et al. recommended oral capecitabine as an adjuvant chemotherapy with ECOG 0, 1 and 2. While considering the palliative chemotherapy only tablet capecitabine or tablet erlotinib was recommended for ECOG 0 and 1. Best supportive care was recommended for ECOG 2, 3 and 4 [16].

In conclusion, gallbladder cancer is a significant public health care problem in this part of the world. Most of the patients presents at an advanced stage. COVID-19 pandemic had created a dilemma among the oncologists, how to manage cancer patients during the COVID-19 pandemic. Systemic chemotherapy increases the risk of morbidity and mortality during active COVID-19 infection. Systemic intravenous chemotherapy further increases the risk of complication in cancer patients. While considering the optimal treatment for the gallbladder cancer the aim should be to balance the risk, benefit of the patient, and health care providers and at the same time considering minimum constraint to the existing health care system. Gallbladder cancer patients may be considered for oral single agent chemotherapy instead of intravenous chemotherapy during this COVID-19 pandemic in presence of preserved ECOG performance status and appropriate indication.

Acknowledgments

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Nil

Conflicts of Interest

The authors have no conflicts of interest to declare.

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REVIEW

COVID-19 in Immunosuppressed and Cancer Patients: A Review

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Abstract

The rapidly spreading outbreak of infection by novel coronavirus 2 (SARS-CoV-2) from Wuhan, China around the world has started since December 2019. Since the epidemic spread of this infection, individuals with comorbidities are at high risk of severe disease and increased rate of mortality. As patients with cancer are considered immunosuppressed caused by some host and treatment factors, a more detailed investigation on the impact of cancer on COVID-19 outcome seems to be necessary. This review article provides data on cancer patients affected by SARS-CoV-2 infection. Although underlying immunosuppression has not proven as a risk factor for severe COVID-19 infection, most authors have identified cancer patients as a highly vulnerable population. We need more detailed especially randomized studies to compare the outcome of cancer and non-cancer patients with SARS-CoV-2 infection. The more precise studies would help oncologists to make the best decision in cancer therapy.

Keywords: COVID-19- cancer- immunosuppression

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Introduction

Several countries from the different continents around the world are experiencing an outbreak of new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2019, coronavirus disease (COVID-19) began in Wuhan, China, and spread rapidly and was reported more than 80,000 confirmed cases with 3000 deaths in China [1]. The two other human coronavirus (HCoV) infection epidemics, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) were reported first in China and Saudi Arabia in 2003 and 2012 respectively [2]. These HCoVs can present with a wide spectrum of respiratory symptoms ranging from the common cold to acute respiratory distress syndrome [3]. Similarly, the clinical presentation of COVID-19 can be mild (no or mild pneumonia) in 81% of cases, severe (dyspnea, hypoxia and lung involvement in radiographies) in 14% cases, and critical (respiratory failure, multiorgan failure or shock) in 5 % of cases [4]. Underlying conditions which have been associated with severe disease and mortality include age more than 65, hypertension, diabetes mellitus, cardiovascular disease, tumor surgery, cirrhosis, parkinson's disease, obesity, and male sex [5-8]. As the covid-19 outbreak grew, concern has raised about the risk of severe disease and increased fatality among immunosuppressed or cancer patients. Our purpose of this study is to review the vulnerability of patients with cancer to SARS-CoV-19.

The role of immune response in respiratory viral infection

Immunopathology of viral infection of the respiratory tract not only is the direct effects of the viral pathogen but also includes the response of the respiratory cells and recruited immune cells of the host [9]. When the mucus layer of the respiratory tract fails as the first line of defence against the viral pathogen, the innate immune system is engaged in eliminating the virus [10]. The innate immune response starts by pattern recognition receptors (PRR) which are sensors for pathogen- or microbe-associated molecular patterns (PAMP/MAMP) [9]. The most

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important PRRs for recognizing the forms of RNA which are produced by respiratory RNA viruses are Toll-like receptors 3, 7, and 8 [11].

Large variety of pro-inflammatory cytokines and chemokines are produced by respiratory epithelial cells including interferon (IFN), interleukin-6 (IL-6), tumor necrosis-factor alpha (TNF-α), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-8 [9]. Type 1 IFN is the crucial cytokine involved in defence against viral pathogen invading the respiratory system [12]. Several antiviral roles of type 1 IFN include stimulating phagocytosis and dendritic cell maturation, significant impact on dendritic cells, and enhancing the activity of lymphocytes [9]. Despite the essential role of IFN in viral pathogen elimination, some adverse action can be induced by IFN such as lymphopenia, tissue injury by expression and release of pro-apoptotic TNF-related apoptosis-inducing ligand (TRAIL) [10]. High viral replication in the respiratory tract may be associated with dysregulated host immune response and the production of plenty of pro-inflammatory mediators [13]. Rapid elevation in pro-inflammatory cytokines/chemokines would increase the recruitment of innate and adaptive immune cells to the lung. In addition, release of these mediators can damage the endothelial-epithelial barrier and alveolar epithelium eventually leads the acute respiratory distress syndrome (ARDS) [9][14]. Therefore, exaggerated host immune response may have a significant role in fatality of respiratory viral infection.

Here, an important question is how exactly immunodeficiency impact the outcome of patients with respiratory viral infection. In a systematic review on risk factors of MERS reported by Park et al. immunosuppressed patients were not at increased risk of mortality due to MERS infection [15]. In a report from a large group of patients with SARS in North America, mortality and morbidity were significant especially among patients with diabetes and other comorbid conditions such as COPD, cancer, and cardiac disease. In that study, immunosuppression was not reported as a risk factor of poor outcome except of patients with cancer [16]. In recent outbreak of COVID-19, Lorenzo D'Antiga reported his experience from a main hospital of Lombardy, Italy, and declared no increased risk of severe pulmonary disease and poor outcome among immunosuppressed patients compared to general population [8].

Respiratory viral infection in cancer patients

Although risk of infection is higher in hematologic malignancies especially during their neutropenic episodes, several factors predispose patients with solid tumors to infection as well. Patients with solid tumors are not generally immunosuppressed, but the factors which damage to the anatomical barriers such as skin and mucosal surface, obstruction, procedures, medical devices or catheters, and cancer treatment (chemotherapy and radiotherapy) would increase the risk of infection in these patients [17]. Respiratory tract is one of the most common site of infection in patients with both hematologic malignancies and solid tumors. The spectrum of pathogens depends on the type of underlying immune deficit associated with malignancy and its treatment. Respiratory viral infection is seen more in patients with impaired cellular immunity including patients who received corticosteroid or chemotherapy containing purine analogues (Fludarbine, Cladribine, or Pentostatine), and recipients of hematopoietic stem cell transplantation (HSCT) on immunosuppressive prophylaxis of graft-versus host disease (GVHD) [18].

Community acquired respiratory viruses (CRV) are common causes of respiratory infection usually lead to common cold in patients without impaired immunity. While, in patients with cancer, pneumonia occurs in 30% of CRV infections with high mortality rate [19]. Potential causes of respiratory viral infections include paramyxiviridae (parainfluenza,respiratory syncytial virus [RSV], and human metapneumovirus [hMPV]), orthomyxoviridae (influenza A,B,C), coronaviridae, picornaviridae ,adenoviridae, polyomavirus type 1, and bocavirus [20]. Although there is some data regarding the presentation and outcome of some CRV such as influenza and RSV in patients with cancer, information on most of these respiratory viruses in these groups of patients is insufficient [19][21].

Coronaviruses infection in cancer patients

Coronaviruses are a large family of single-stranded RNA viruses, which were denominated for their corona-like morphology on electron microscopy [22]. CoVs can infect both animals and humans, causing respiratory, enteric, hepatic and central nervous system diseases [22][23]. Gerna et al. have shown that among 823 patients were hospitalized for respiratory infection, 5.7% were found to be infected by coronavirus. Surprisingly, in that study all infected adults were immunocompromised [24].

Although it is well known that individuals affected by cancer may be more susceptible to severe pulmonary viral infection, cancer and coronavirus infection still has not been well-studied field. Only, there is some small reports in recipients of HSCT who developed severe pulmonary infection. In a case report, Folz et al documented coronavirus infection in a young woman with breast cancer who developed pneumonia following autologous bone marrow transplantation (BMT). They recommended consideration of CoV in the differential diagnosis of pulmonary symptoms in recipients of high dose chemotherapy and autologous BMT [25]. Another case report published in 2012 was a 38 years old woman who underwent autologous hematopoietic stem cell transplantation for severe systemic lupus erythematous. The patient died 26 weeks after transplantation following treatment as influenza for her presentation of pulmonary infiltration and hypoxia. Finally, HCoV RNA was identified in bronchoalveolar lavage fluid (BAL) at autopsy [26]. Milano et al. reported 11% the day100 cumulative incidence of HCoV infection among recipients of allogeneic hematopoietic stem cell transplantation which was in second place between other viruses after human

rhinovirus. Despite the high incidence of HCoV infection among recipients of HSCT, morbidity and mortality was low in their cohort study and none of the patients with coronavirus developed lower respiratory tract infection [27]. Hakki et al. have also found the high incidence of CoV infection among patients who underwent HSCT, 9.7% of infection episodes which was in third place after rhinovirus and enterovirus. Similar to Milano et al. study, possible and proven lower respiratory tract infection was lower in coronavirus infection compared to other types of virus [28].

How cancer and chemotherapy impact the COVID-19 outcome?

As the COVID-19 spread rapidly, concern has raised about the patients with cancer and who are on anticancer treatment. These patients might be at significant risk of severe COVID-19 and poor outcome. Data about the impact of two previous coronaviruses infection outbreak (SARS and MERS) is limited. In a Canadian retrospective case series involving 144 patients with SARS, 21-day outcome was described. They reported 8 deaths in their cohort of 144 patients (21-day mortality of 6.5%) which one of 8 died patients had cancer [16]. Although in Korean study malignancy was not associated with increased case fatality rate (CFR) in patients with MERS [29], Jazieh et al. have reported increased CFR resulting from MERS-CoV infection among patients with cancer (only 3 patients with early stage cancer from a total 19 patients with cancer survived) [30]. There are significant variations in the predictors of mortality in MERS patients between different studies. Malignancy was reported as one of the risk factors of death in some of these studies [15].

In the recent coronavirus outbreak, COVID-19, many questions about patients with cancer have still remained. Many cancer institutions are confounded about the treatment plan of these group of patients during present pandemic. A prospective cohort on COVID-19 patients in China, 18 of 1590 COVID-19 cases had a history of cancer which was more than the incidence of cancer in general population in China. The most common cancer type was lung cancer. Also, patients with cancer have found to have poorer outcome [31]. The experience from a cancer institute in Italy has been reported by Trapani et al [32]. They identified nine cancer patients diagnosed by COVID-19. Only two of nine patients showed severe pneumonia and none of these patients with severe COVID-19 was receiving immunotherapy, considered as a risk factor for serious COVID-19.

A multicentre study from 14 hospitals in Hubei Province, China, described the clinical characteristics and outcome of 536 COVID-19 cases without cancer and 105 hospitalized COVID-19 patients with cancer [33]. They revealed that patients with cancer had poorer outcome compared to non-cancer patients. In that study, outcome of the COVID-19 was influenced by tumor type, and patients with hematologic malignancies had more aggressive course compared to patients with solid tumors.

Another retrospective cohort study by Zhang and colleagues has represented clinical outcome of 28 cancer patients among 1276 COVID-19 patients admitted in three hospitals in Wuhan. The mortality rate of this patients was 28.6% which was much higher than fatality rate of COVID-19 in general population of China (2.3%) [34].

Conversely, some small studies have represented milder symptoms in patients with cancer. for instance, Guan et al. extracted data of 1099 patients infected by HCoV-2 and found only 10 patients with history of cancer (0.9% of all patients). Most of these patients had mild symptoms (7 of 10 patients) [35]. Another study represented the severity assessment of 69 patients with COVID-19 by SpO2. Severe disease (SpO2<90%) was seen in only 0ne of 4 cancer patients which was comparable to total cases of study [36].

Although most of these studies are retrospective and nonrandomized and have different results, some of them support the vulnerability of patients with cancer in this coronavirus pandemic. There is great uncertainty in healthcare system involving the cancer patients about the management of cancer during the pandemic. Beside the susceptibility of cancer patients to severe COVID-19, there are some limitation in the management of cancer patients during pandemic as well, including shortage of blood products, involving most staffs in COVID-19 centres, postponing their appointment especially due to travel restriction, and misgiving about the treatment of cancer. Despite all of the mentioned controversies about the outcome of patients affecting by COVID-19, many cancer institutions around the world publish some guidelines in the management of cancer patients during the pandemic. Some important factors involving in the decision about cancer therapy include cancer prognosis, cancer stage, treatment setting (adjuvant, neoadjuvant, or palliative), type of cancer treatment (intravenous versus oral chemotherapy, radiotherapy, or surgery), impact of delay, modify or interrupt the chemotherapy on cancer outcome, probability of COVID-19 infection, and patient comorbidities.

In Conclusion, the issue of cancer and COVID-19 is not yet well studied, including only some small Italian and Chinese series and retrospective studies. Many questions have remained without clear answer. Representing the cancer as a risk factor for severe COVID-19 and poor outcome by authors have raised the concern about the decision about the cancer therapy. Certainly, we need more detailed studies on cancer and COVID-19 to determine the impact of cancer therapy on outcome of COVID-19 and the effects of this pandemic on treatment of cancer.

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REVIEW

A Comprehensive Review on the Working of a Radiation Oncology Facility During the Covid-19 Pandemic and Adapting it for South Asian Settings

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Abstract

Background: With the pandemic gaining a firm foothold globally, various governments world-wide are trying hard to halt its unprecedented spread. The pandemic is challenging the healthcare professionals in unique ways and forcing the frontline fighters to come up with dynamic changes in almost all disciplines of medical science. This article is aimed at a detailed review of the existing guidelines for radiotherapy practice during this pandemic from across the world. **Methods:** This review has been organised under specific subheadings that pertains to the functioning of a Radiation Oncology facility in South Asian countries like India. After a detailed Zoom video conference between the authors, it was decided to focus the review under the following subheadings: staff allocation, staff education, screening of patients, patient waiting area modification, patient selection, radiotherapy planning and execution, review of patients on radiotherapy, brachytherapy, inpatient admissions, follow up, resident training and treatment of suspected or positive COVID-19 patients. **Results:** After discussion among the authors, a consensus working suggestion during the COVID-19 pandemic has been proposed for a radiotherapy center in a South Asian country like India. All the authors worked simultaneously on a Google doc document to develop this manuscript. **Conclusions:** This paper can be a reference document for the functioning of a radiotherapy facility during the COVID19 pandemic. As the infrastructure of different institutes vary and so does each patient, the importance of fine tuning and tailoring our final decisions before treating a patient in this unprecedented crisis cannot be undermined.

Keywords: COVID 19- Pandemic- Radiotherapy- External Beam- Brachytherapy

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Introduction

Ever since the first case of Novel Coronavirus was reported from China, by the World Health Organization (WHO) on 31st of December 2019, it has spread to various countries. The biggest impact has been on the healthcare system. In India the first case was reported in a student from Kerala who had returned from Wuhan on the 30th of January, 2020. India reported its first death on 12th March in a 76 year old man who had returned from Saudi Arabia. Despite stringent measures, there is a linear rise in the number of infections. Not only are cancer patients more susceptible to COVID-19, they also are at a higher risk of suffering from severe events like ICU admissions

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requiring ventilation, or death [1]. The world had already seen the catastrophic consequences that the pandemic had on countries which are known for their premier healthcare delivery systems like Italy, the United States and the United Kingdom. It is imperative that we learn from their experiences. These advisories and contingency plans are intended to cover in depth the nuances of running a radiation oncology department in South-Asian countries.

Materials and Methods

The authors did a thorough literature search in PUBMED and Google looking for published articles relating to COVID-19 and Radiotherapy. The websites of all important oncology Journals, directives from the Oncology societies and different institutional guidelines were also searched. The authors conducted video conferencing meetings using the Zoom App and the broad headings for the article being written was agreed upon. The manuscript was worked on google docs simultaneously by the authors from their respective places. Our approach of teleconferencing and shared document platforms is all the more important at this juncture when physical distancing is the new norm. At the time of writing this paper there were 38 publications, 6 society guidelines and 10 institutional guidelines available. This review will be covered under 13 sub headings:

Results and Discussion

Staff Allocation

Published guidelines: Radiotherapy centres in Wuhan had created an ad-hoc emergency infection control team responsible for activities related to control of infection [2]. Staff members comprising Radiation Oncologists, Radiation Therapists and nurses were divided into groups of A and B, each working for a specified number of days followed by 7-10 days break, the estimated incubation period, to avoid exposure simultaneously [2]. Experience from Singapore highlighted the importance of segregation of staff even at work, like separate areas and timing of meals for each staff [3]. NICE (2020) guidelines from the UK suggests that those HCW who have to self-isolate themselves can help with remote tele consultations, contouring, and communications [4]. A system-wide "COVID Huddle" video-conference daily was suggested at John Hopkins [5]. Italian experience proposed borrowing staff from other facilities and to call back retired staff, to continue services [6].

Policy that can be implemented:

1. Formation of a "COVID-19 emergency team" including the head of the department for dynamic monitoring of policy, addressal of staff problems, PPE availability and if needed, change in policies.

2. Meetings at least twice a week (by video conferencing) with all working staff for feed-back, functioning and safety.

3. If adequate strength available, all staff may be divided into 3 teams- Team A, Team B and Team C. Team A and B can work by rotation for a minimum of 7 days each. When Team A is working, Team B works from home, assisting in remote conference patient visits, remote contouring and planning. TeamC are deployed in essential COVID-19 duties.

4. Remote access licences for the treatment planning systems need to be worked out with the vendors.

5. Divide RT area into different zones based on contamination levels. The respective areas are to be disinfected accordingly. Efforts must be taken to ensure minimal intermixing of staff posted in respective areas.

6. Discourage staff borrowing as the staff strength is already compromised and the legal issues involved. Take all measures to protect the staff from infection to continue services.

Staff Education

Published guidelines: Detailed guideline has been provided by the WHO (2020) which covers hand washing, respiratory hygiene, physical distancing, self quarantine for those with travel history, which must be practiced by all, including a HCW. Guidelines on rational use of PPE has been published by the Ministry of Health and Family Welfare (MOHFW) Govt. of India [7].

Policy that can be implemented:

1. Demonstrations of proper PPE usage and disposal, behavioral changes to be adopted including physical distancing, hand hygiene and respiratory etiquettes both while dealing with a patient and outside the hospital, must be given to all staff, preferably by an expert from the infection control team.

2. They can be trained by the medium of presentations, mock drills and telemedicine.

3. Emergency preparedness and contingency plan should be discussed

4. Physical distancing among the HCWs and patients has to be followed strictly at all times including tea times and lunch breaks.

Screening

Published guidelines: Very stringent screening of patients was done in Wuhan. Masks were compulsory. Patient and attender would first go through a temperature checkpoint. At John Hopkins also an intensive screening was followed for respiratory symptoms which if present, patients were assigned to a specific primary health care. [5]. A policy of bracelets for screened patients was followed by Italian centers [8]. In certain centers in Washington, thermal scanners were installed in entrances [9]. In Iranian centers, health workers were required to change clothes at entry and exit [10]. In Taiwan, if the patient has travelled to a hotspot zone in the last 2 weeks, then they were prohibited from entering hospitals till completing a 14-day quarantine [11].

Policy that can be implemented:

1. A queue with physical distancing (marked as circles for standing) should be drawn before all entryways. Patient alone or maximum one caregiver be allowed.

2. The wearing of masks must be compulsory for both the patient and the caregiver. Hand wash and sanitization for every person entering and exiting the building must

be made compulsory.

3. A self-declaration form which includes travel history, contact history, respiratory symptoms and fever is to be filled by patient and caregivers. A declaration that they may contract infection during treatment can be signed. Online forms that can be filled and submitted by the patient from their mobile is preferred to decrease the chance of infection associated with paper forms. [appendix A1] & (https://form.jotform.com/201074359399463).

4. Thermal scanning with a hand held non touch thermometer is advised..

5. A separate entry and exit for patients may be provided.

Waiting Area

Published guidelines: Italian centers modified the waiting areas with each chair being spaced more than 1 metre and articles like magazines and newspapers removed from the waiting area [8]. The Iranian experience highlighted separate isolated waiting areas for those who had symptoms of cough, fever or unexpected malaise or myalgia. If the number of people had exceeded the capacity of the waiting room, they were advised to sit in their cars or areas outside the hospital [10]. NICE guidelines have highlighted the importance of scheduling a patient carefully, such that the patient does not have to wait for a prolonged time unnecessarily [4].

Policy that can be implemented:

1. Decrease the number of chairs available in the waiting area, spacing at least one meter between chairs.

2. Pictorial depiction of personal etiquettes like handwashing, respiratory hygiene and physical distancing can be displayed on the walls of the waiting area.

3. Careful scheduling of time-slots for treatment/simulation is mandatory to minimize undue delay for treatment and decrease the time spent in the waiting area.

4. Waiting area has to be sanitized frequently

Patient Selection

Published guidelines: The UK NICE (2020) have given comprehensive guidelines for selection of patients for radio-therapy and divided patients into 5 groups [4]. The highest priority was given to the rapidly growing tumors like that of head and neck, cervix, and post operative with residual disease; least priority given to prostate, and hormone positive breast cancers. The RADS (Remote, Avoid, Defer, Shorten) principle had been advocated. John Hopkins University divided patients into different levels from 1 to 3. Level 1 are those that would continue radiation. This includes those who were already on radiotherapy and those who require urgent radiotherapy in a palliative setting or rapidly proliferating tumor in curative setting. Level 2 includes routine sites that require radiotherapy. Level 3 included those cases where RT could be delayed or omitted altogether [5]. For Head and neck cancers, concurrent chemotherapy can be omitted for patients 70 years or older with co-morbidities, such as diabetes and cardiovascular diseases. Chinese centers did not prioritize as less patients visited the facility due to lock down.

Policy that can be implemented:

1. Patients in whom to avoid radiotherapy altogether:

a. Hormone positive, elderly women with carcinoma breast post breast conservation surgery and started on hormonal therapy.

b. Palliative radiotherapy in patients with ECOG of 3 or 4 (very unlikely to benefit).

c. Defaulted patients due to personal, logistic or post-operative complications, who have presented for post-operative radiotherapy where the window of benefit has passed.

2. Patients in whom to delay radiotherapy:

a. Carcinoma prostate, kept on Androgen deprivation therapy (ADT)

b. Carcinoma Breast: If adjuvant radiotherapy is indicated, a delay of up to 6 to 7 months after surgery and 1 month after adjuvant chemo is acceptable. For hormone positive tumors, hormone therapy can be started and a slightly longer delay may be acceptable.

c. Head and Neck Cancers: In patients started on neoadjuvant chemotherapy, with good response and tolerance, RT can be delayed with 2 or more additional cycles of chemotherapy. Post op radiotherapy in salivary gland tumors may be prolonged.

d. GI cancers: Adjuvant radiotherapy in carcinoma of rectum, stomach, pancreas and gallbladder may be delayed and adjuvant chemotherapy can be started.

e. Brain tumors: Grade 2 tumors post complete excision may be advised for delayed radiotherapy and follow up. For those with incomplete excision or grade 3 tumors and certain elderly patients with grade 4 gliomas may be started on Temozolomide for 2 to 3 cycles to delay radiotherapy. Radiotherapy maybe differed for benign tumors like meningiomas and arteriovenous malformations.

f. Sarcomas: Most low or intermediate grade sarcomas may be considered for delayed radiotherapy. Ewing's sarcoma and Rhabdomyosarcoma can continue chemotherapy till the control of the pandemic.

g. Carcinoma Lung: Those receiving neoadjuvant chemotherapy, with good response, may be continued for a few more cycles, before start of radiotherapy. Prophylactic cranial irradiation in small cell lung cancer may be delayed or avoided.

h. Palliative radiotherapy: For patients with no acute symptoms that need palliation, RT can be delayed. Also for bone metastasis in non-weight bearing sites with adequate control of pain with analgesics, RT may be delayed.

3. Patients in whom radiotherapy must be given:

a. Patients already on radiotherapy should continue radiation. They can be considered for modification to a hypofractionated regimen.

b. Rapidly proliferating tumor (head and neck, cervix, anal canal, esophagus, inoperable vulva and vagina, post operative with residual disease in fast growing tumors, young grade 4 gliomas).

c. Urgent palliative radiotherapy which gives good symptomatic relief, such as malignant spinal compression,

superior vena cava syndrome or bony pain.

d. Adjuvant radiotherapy may be given with low priority if local recurrence risk is more than 20% at 10 years.

Radiotherapy Fractionation

Published guidelines: The most established fact is that "shorter the treatment, the better", which highlights the importance of hypofractionation [12-13]. For breast cancer, the guidelines for the pandemic have evolved rapidly. Hypofractionation with a dose of 40 Gy in 15 fraction and 42.5 Gy in 16 fraction has been the most accepted regimens. Extreme hypo fractionation has also been adopted in many centers with a dose of 26 Gy in 5 fraction. Boost has been avoided in those less than 40 years of age. External beam Partial breast irradiation of 40 Gy in 10 fraction or 30Gy in 5 fractions has also been adopted [14]. For carcinoma of rectum short course radiotherapy is preferred. In certain centers, organ preservation is also advocated with surgery reserved as salvage for recurrence [15]. In head and neck, definitive chemo-radiation should be given along with simultaneous integrated boost (SIB) techniques in the standard (5 fractions per week) or accelerated schedule (6 fractions per week) in order to achieve a 1-week reduction compared to sequential technique [16]. RCR suggested to consider 65 Gy in 30 fractions or 55 Gy in 20 fractions over standard 70 GY in 35 fractions with limiting chemotherapy over 60 year.

Policy that can be implemented:

1. Carcinoma Breast: Extreme hypofractionated regimens like 28-30 Gy in 5 weekly fractions, (FAST protocol) or 26 Gy/5 Fractions/ 1 week (FAST forward) may be given preference if radiotherapy is planned. If these are not possible, 40 Gy/15fr/3weeks may be used instead of conventional regimens. Avoid boost dose for all. If at all compulsory, go for a simultaneous integrated or 10 Gy/ 4fr/ 4 days sequential boost (for <40 years only). Encourage external beam accelerated partial breast irradiation (APBI) protocol of 30Gy/5 Fractions in suitable patients.

2. Head and Neck Cancers: A dose of 65Gy / 30 fr/ 6 weeks by SIB-IMRT technique is advocated instead of 70 Gy/ 35 fr/ 7 weeks. A dose of 60-64Gy in 30-32 fractions is used in postop settings. Concurrent chemotherapy to be avoided above 60 years.

3. Carcinoma Cervix: 50 Gy in 25 fractions followed by a 3D IMRT/ SBRT boost of 10-16 Gy (If brachytherapy not possible). Concurrent chemotherapy to be given.

4. Carcinoma prostate: It is better to delay prostate radiotherapy at this time. If planned they can receive 60Gy in 20 fractions over 4 weeks. SBRT protocols may be given priority over moderate hypofractionation in localized disease, if the logistics for planning and delivery permit.

5. GBM: 25Gy/5Fr/1 week may be given if RT is considered.

6. GI malignancies: There is no role of hypo-fractionation in these settings and are treated in the conventional dose fractionations of 45-54Gy in 1.8-2Gy per fraction, except in rectum, where preop short course RT of 25 Gy in 5 fractions can be given.

7. Carcinoma Lung: Conventional fractionation will be followed up to a dose of 60Gy in 30 fractions over 6 weeks. Prophylactic cranial irradiation may be avoided or delayed.

8. Palliative radiotherapy: 8 Gy in single fraction should be advocated for spinal cord compression, impending fractures and severe bone pains. For SVCO one may consider 8.5 Gy weekly for two fractions. Brain metastases may be considered for whole brain radiotherapy of 20Gy in 5 fractions.

Treatment Planning and Execution

Published guidelines: Italian experience described how CT simulation of patients was dispersed at different times of the day, to decrease waiting outside CT-simulation room [8]. Most published guidelines advocate treatment as less complicated as possible. For those patients who have started treatment with active breath coordinator (ABC) can be completed using the same unless the patient becomes COVID-19 positive. It is advisable not to start any new patients with ABC during this time [17]. Experience from Switzerland highlights the need for making less complicated plans, and limits the use of complicated IMRT, SBRT and SRS only if necessary, as this would avoid the need for patient specific quality assurance by a medical physicist [18].

Policy that can be implemented:

1. 2 Dimensional planning in telecobalt or a linear accelerator should be preferred if possible, as the treatment can be started on the same day and less manipulation on the machine during setup. Hypofractionated treatments may be given with conformal and image guidance techniques.

2. CT-based planning may be done only for carefully selected patients. Special care must be taken while placing fiducials, giving oral contrast (ca esophagus), intravenous contrast, specially after cross checking past history of allergy to avoid unnecessary need for resuscitation in case of anaphylaxis.

3. Licences for remote planning and contouring may be obtained from the vendors.

4. Each planning, treatment and set-up should be followed by appropriate disinfecting of the surface of the couches, immobilization devices, other radiotherapy accessories like head rests, knee rests, breast boards, baseplates thermoplastic masks, etc with appropriate disinfectants like 1% sodium hypochlorite. Care should be taken to frequently disinfect the mouse and keyboards.

5. Thermoplastic casts of each patient should be kept separately.

6. Skin marking is preferred for all palliative patients as this helps in avoiding unnecessary contact with staff for making thermoplastic sheets and avoids need for sanitization of baseplates and casts.

7. History pertaining to symptoms of COVID should be asked every day by the technical staff before taking the patient for treatment. Any COVID-19 positive/suspected patient should have their treatment stopped and restarted only after 2 negative results.

8. The total number of patients on the machine needs to be restricted and spread out with intervals to avoid crowding and to give time for sanitisation in between.

9. Avoid complicated treatment planning, like stereotactic body radiotherapy (SBRT), SRS as it can increase the risk of transmission (longer and multiple interactions, longer treatment setups and added radiotherapy accessories).

10. Avoid using ABC.

Review of Patients on Treatment

Published guidelines: Although specific guidelines have not been published specifically for reviewing patients on radiotherapy, it has been encouraged to have maximum review and follow up through tele-communications, WhatsApp or video-conferencing.

Policy that can be implemented:

1. Reviewing of patients on treatment should be as minimal as possible, and can be encouraged by tele-communication or video conferencing platforms like whatsapp, preferably by HCW working from home.

2. For physical review, a minimum of 1 to 2 meter distance has to be maintained between patients presenting with such symptoms.

3. Patients coming for review may be advised to come alone without any attendant, unless the patient is a child, sick or has difficulty in comprehension.

4. Routine blood investigation may be avoided unless absolutely necessary.

Brachytherapy

Published guidelines: The most important one is the ABS (American Brachytherapy Society) (2020) guideline, which gives strict instruction to continue the treatment of carcinoma cervix in patients whose treatment has already started and high risk carcinoma prostate planned for EBRT and Brachytherapy boost [19]. Endometrial cancer requiring brachytherapy may be delayed till 12 weeks, however 9 weeks is recommended. Experts from Switzerland had anticipated the shortage of anesthetists and recommended sedoanalgesia (sedation plus local anesthesia). They also increased EBRT dose to avoid brachytherapy. RCR has proposed adapting the treatment pathway to deliver 2 to 3 fractions per insertion with 6 hours gap.

Policy that can be implemented:

1. In cervical cancers, all the three fractions can be delivered with a single applicator insertion keeping the patient admitted with the radiotherapy delivered 6 hours apart, instead of weekly fractions. Alternately 9 Gy x 2 weekly (PGIMER regimen) may be given.

2. Insertions may be performed under sedation rather than spinal or general anaesthesia.

3. Vault brachytherapy may be continued.

4. Endometrial cancer brachytherapy in intermediate risk should be avoided.

5. Interstitial implants to be avoided as it will require anaesthesia, which may not be available.

6. Replace Interstitial implants with external beam radiotherapy (EBRT).

7. Brachytherapy for prostate cancer is not justified in this pandemic and may be avoided.

8. Head and neck brachytherapy, Intraluminal brachytherapy for esophagus and lungs are strictly prohibited.

9. Breast brachytherapy may be avoided and replaced with EBRT.

Inpatient Admissions

Published guidelines:

There is paucity of data regarding criteria for admissions, although the requirement would be low. Chinese had a very strict policy regarding admission with every patient and attender being screened with CT chest, and all symptomatic patients being tested for COVID 19, and admitting only if negative [2]. Italian experience in pediatric oncology suggests a single parent accompanying the child, a single child in recovery after GA and sterilization of all toys on a daily basis [20].

Policy that can be implemented:

1. All patients requiring admission must strictly be screened, with a very low threshold for COVID-19 testing.

2. The number of beds in a cubicle may be restricted to follow strict physical distancing guidelines.

3. For those requiring admissions like radiotherapy under GA and very sick patients like SVCO syndrome, symptomatic brain metastasis etc, all admissions are to be considered only after thorough screening of patients and attenders along with COVID-19 testing for any suspicious patients. A compulsory CT scan may not be feasible or justified in view of the radiation risk and contamination.

4. All admitted patients and attenders should be given proper health education, encouraged to wear face masks and have their hands sanitized periodically.

Follow up Policy

Published guidelines: All published guidelines strongly recommend tele-communication and video consultations. Patients with prior appointments may be contacted to postpone them.

Policy that can be implemented:

1. Teleconferencing platforms like Whatsapp can be used as the primary modality of communication.

2. Patients should be educated regarding the signs and symptoms of recurrence or disease progression.

3. Follow up investigations like Whole Body PET-CT, MRI, CECT, DEXA scans, 2D ECHO, blood investigations etc may be postponed.

4. Remedies for radiation reactions and adjuvant treatments like hormonal therapy may be advised over teleconference.

5. The frequency of followup may be decreased.

Resident Training

Published guidelines: United States groups did focus on resident training. All lectures and didactic activities had been converted to videoconference.

Policy that can be implemented:

1. Academic training should be started through video-conferences.

2. Residents may be encouraged to use their spare time judiciously when 'working from home' to focus on studies and writing research grants and manuscripts for publications.

3. Assessments may be postponed or may be conducted carefully following norms.

Radiotherapy Treatment of Covid-19 Suspected or Positive Cancer Patients

Published guidelines: According to RCR UK (2020), COVID-19 suspected patients should follow standard norms as for other COVID-19 patients with an oncology team at close reach [21]. If a patient is infected in between treatment, further treatment should be interrupted till cured of infection and treatment restarted after gap correction. As per John Hopkins, suspected or positive patients should only be treated if they meet the criteria for urgent RT, and they are the patients with rapidly progressive curable disease, symptomatic metastatic disease with life expectancy of at least 3-6 months in whom alternative treatment is not possible. These treatments should be done at the end of the day, with appropriate PPE, entry and exit from low volume entrance and following all infection prevention control measures [5].

Policy that can be implemented:

Due to lack of isolated RT facilities and keeping in mind the risk of contagion to other fellow departments, suspected or positive cases should not be treated until they are cured.

All decisions should be taken tailoring to the specific needs of the patients based on the present situation of the pandemic and available resources at the center. One may have to accept the compromise in the overall survival of these patients in these uncertain times.

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REVIEW

Cancer Pain Management in the Era of COVID-19 Pandemic: Concerns and Adaptation Strategies

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Abstract

Pain is a troublesome issue in most of the cancer patients. Under treatment of pain can lead to poor quality of life in them. Thus, it is important to maintain continuity of cancer pain management even during a pandemic situation. In literature, the strategies for adopting the cancer pain management practices in light of current scenario of pandemic are not described. The outbreak of Novel corona virus infection (COVID-19) has imposed multiple challenges including restriction of access to routine health care system, psychological stress and impositions of strict infection control strategy. In this narrative review, we discuss the potential considerations of conventional cancer pain management model during outbreak of COVID -19. Effects of common analgesics on immune system have been described backed by evidence in literature. We provide a few strategies for the cancer pain management practices, which can be adopted during the pandemic. They are prioritization of patients for in-hospital visit, considering biological interactions and legal limitations while prescribing medications, considering only urgent cases for pain interventions and providing a holistic care with use of digital technology. Further good quality randomized controlled trials and formulation of international consensus guidelines is the need of the hour and is highly recommended.

Keywords: Cancer pain- pandemic- concerns- adaptation- COVID-19

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Introduction

Cancer is a major global health problem. As per the World Health Organization (WHO) cancer is the second leading cause of death all over the world [1]. Majority of these patients live with chronic pain due to malignancy. Almost 50% patients with malignancies and 70% patients with advanced malignancies live with the curse of cancer pain [2-3]. Among these, 50% patients suffer from moderate to severe pain, while 25% suffer from more severity of pain [4-6]. Oncological treatments are also associated with acute pain syndromes in cancer patients with chronic pain, e.g. post chemotherapy oral mucositis, chemotherapy induced peripheral neuropathy, radiotherapy induced bone pain, intervention related pain after biopsy or surgery etc [7]. Cancer pain is a complex pathophysiological process. Its exact aetiology is still uncertain, but there are multiple possible mechanisms behind it. It involves visceral, somatic and neurogenic components [8]. Thus the management requires a step wise multimodal therapies to control this complex process. But often our cancer patients remain undertreated for their pain. As per the review of existing literature by Deandrea (2008) nearly one of two patients has under treatment of cancer pain [9]. This under treatment of pain leads to a poor quality of life in cancer patients [10]. Thus managing pain is a priority in cancer patients not only for physical well-being but also for psychological and ethical needs of the patients.

Unfortunately, we are standing amidst a pandemic right now. On 11th March, 2020 the World Health Organization (WHO) has declared the outbreak of novel corona virus (COVID-19) as a global pandemic [11]. Aggressive contact tracing, identifying infected people and maintaining social distance are the major strategies for containment of infection. Many nations have imposed

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strict lockdown measures, which has made the access to the conventional health care systems difficult for the patients. Routine practice for cancer patients has also curtailed down in view of less manpower and to decrease footfalls of patients in the hospitals [12]. Only high priority patients are considered for routine or emergency oncological treatments [13]. Similarly we need to analyse the conventional cancer pain management approach in light of this pandemic situation. This can help to formulate a strategy to maintain continuity of pain management in cancer patients during a pandemic.

We performed a literature search through common search engines, e.g. Medline, Cochrane library and Google scholar using the following key words: 'Cancer', 'pain', 'COVID-19', 'Pandemic'. We could not identify any consensus guidelines or documents describing the concerns and changes in practice for cancer pain management in the context of recent or old pandemics. Thus we here present a narrative review on the aspects of conventional cancer pain management which can be potentially affected by the current pandemic situation. We also suggest some adaptation strategies which can be helpful for a cancer pain management centre.

Conventional model of cancer pain management

The cornerstone of traditional management of cancer pain is a pain ladder proposed by the WHO in the year of 1986 [14-15]. It was a three step ladder (Figure 1) for control of cancer pain [16]. In the first step, the treatment begins with a non-opioid medication. If not controlled, one needs to proceed to the second step to prescribe weak opioids along with non-opioids analgesics with or without adjuvants. If the pain is still uncontrolled, one can move towards the thyroid step where strong opioids can be prescribed and with adjuvants and non-opioids analgesics. The basic principle of prescribing drugs for cancer pain is:

- It should be by the mouth preferably.
- IT should be prescribed round the clock.
- It should be individualized.
- It should be titrated according to the individual patient's pain score.

Over the past three decades, this ladder approach has been criticized and modified in many ways. One of the major adaptations is the addition of a fourth step to the ladder (Figure 2) advocating use of interventional pain procedures as appropriate [17]. These interventions include invasive techniques, neurolysis, neuraxial implants, neurosurgical techniques etc. This bidirectional ladder approach helps the physicians to manage acute pains associated with cancer along with chronic pain [17]. Later, debate sprouted for use of an intervention at an early stage of cancer pain. Amr and Makharita (2014) performed sympathetic plexus nerve blocks for inoperable abdomino-pelvic malignancies at an early stage, before the second stage of WHO ladder [18]. They found it had a better control of pain, lesser opioid requirements and better quality of life as compared to those patients who were treated with the conventional therapies. But, there is lack of large scale quality trial which proves benefits of early integration of invasive pain procedures in cancer patients. So, the most practiced approach is to start with a conventional approach and gradually opt for a more invasive procedure. Individualized strategies for interventional pain management at an early stage of cancer pain is highly desirable [19].

Among the medications, the most commonly used drugs for cancer pain can be divided into three categories: Opioids, non-opioids and adjuvant analgesics. The opioids again can be classified into two for practical purposes: a weak opioid for step 2 and a strong opioid for step 3.The weak opioids which can be used in step 2 are: tramadol [20], codeine [21] and tapentadol [22]. The strong opioids include morphine, methadone [23], fentanyl [24] , buprenorphine [25] etc. Though the oral preparations are preferred, other preparations have also been found useful for managing moderate to severe cancer pain, e.g. intravenous, subcutaneous [26], sublingual [27] or transdermal [28].

The non-opioid analgesics are being prescribed at all the steps of the ladder from 1 to 3 [29]. The two such common drugs are acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDS). The NSAIDS are particularly useful for somatic and bone pain due to its anti-inflammatory action [30]. But, unfortunately it has

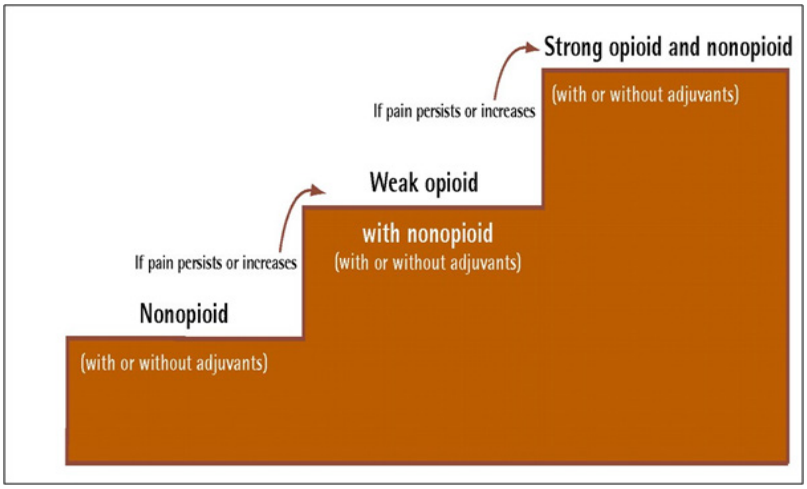

Figure1. The Original World Health Organization Pain Ladder (Adopted from World Health Organization, 1987)

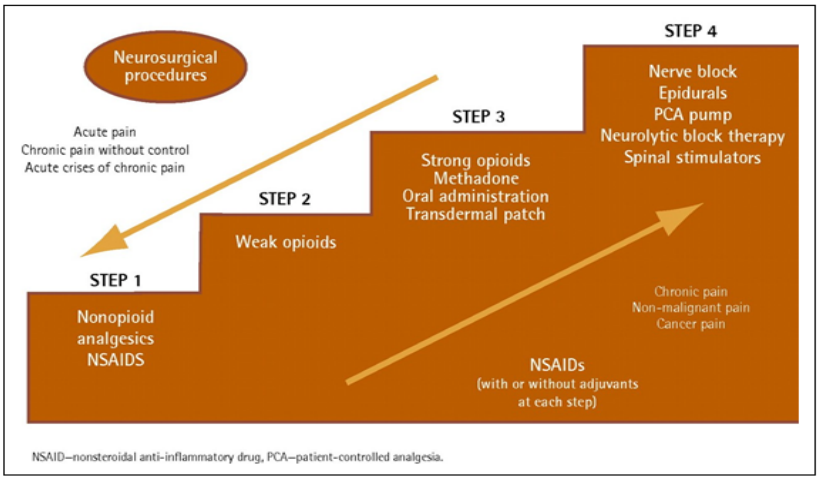

Figure 2. New Adaptation of WHO Pain Ladder (Vargas-Schaffer G (2010), Reprinted with permission)

some side effect profiles, e.g. Gastrointestinal bleeding, thrombocytopenia etc [30]. In such patients with refractory bone pain, a palliative radiotherapy should be considered [31]. The third class of drugs used for managing cancer pain are various adjuvant drugs. These drugs with multiple mechanisms of actions have been found especially useful for a neuropathic or mixed type cancer pain. Some of these are anxiolytics, antidepressants [32] antiepileptic [33], N-methyl-d-aspartate (NMDA) receptor antagonists [34], steroids, cannabinoids [35] etc.

Biophysiological considerations of conventional cancer pain management during COVID 19 outbreak

Cancer patients are at high risk of COVID-19 infection. In a nationwide analysis in China by Liang et al, 2020 showed that patients with cancers have a higher incidence (1% vs. 0.29%) of severe COVID-19 infection than general population [36]. In another multicentric study [37] cancer patients were found to have higher overall 30 days mortality and it was associated with risk factors specific to cancer. Thus, any therapy in cancer patients including pain management needs special considerations regarding their immunomodulatory effect. A negative immunomodulatory effect is to be avoided as it may lead to a high viral load and more complications in cancer patients. Thus, we here focus on possible immune interactions of common pain medications described in literature.

1. Opioids

Opioids are the backbone of managing moderate to severe cancer pain. But their effect on immune system remains controversial. Long term therapy with opioids for chronic pain has been found to supress the immune system [38]. Long term opioid abusers also have been found to have an increased rate of infections [39]. Multiple mechanisms of immunosuppression by exogenous has been suggested e.g. interaction with both innate and acquired immunity [40], effect on hypothalamic pituitary adrenal axis [41], effect on endocrinal systems [42] etc. Large dose and prolonged duration of therapy with opioids have a more pronounced effect on endocrinal system [43]. Different opioids have different effect on immune system. Morphine [44] and Fentanyl [45] suppress the immunity the most; whereas Buprenorphine has a better response in immunocompromised persons [46]. Large dose and prolonged duration of therapy with opioids have a more pronounced effect on endocrinal and immune system [43]. Thus, we can conclude that one needs to be cautious with the patients on high dose of chronic opioids therapy for cancer pain. They need to follow the preventive precautions from Covid-19 infection more stringently.

2. Non Opioid Analgesics:

NSAIDS are widely used for somatic and bone pain related to cancers. There are some controversies regarding use of NSAIDS in COVID patients. In large trials, NSAIDS have been found to increase the complications due to respiratory infection [47]. Indomethacin, a potent NSAIDS, potentiates the expression of the angiotensin converting enzymes (ACE2) and is hypothesized to increase the COVID-19 infection [48]. In a contrasting study result, indomethacin was found to supress viral load in vivo and in vitro against COVID 19 [49]. In hospitalized patients with COVID-19, a high proportion of patients are at high risk of developing AKI [50] due to fever and dehydration. This can be accentuated by the nephrotoxic property of NSAIDS [51]. Though inference from existing indirect links in the literature suggests a caution for use of NSAIDS in COVID-19 patients [52] there is no direct evidence of harmful effect of NSAIDS in COVID-19 patients.

3. Adjuvant analgesics

Steroids are useful adjunct to treat pain related to neuropathy [53], radiation induced pain flare [54], brain metastasis [55] and spinal cord compression [56]. Though steroids showed positive impact on immune system in majority of the literature [57-58], in some studies it showed an increase in viral load [59-60]. Thus it needs to be used with caution in suspected or confirmed COVID-19 cases.

Table1. Summary of Adaptation Strategies

Strategies for cancer pain managment during COVID-19:
Strategies for in-hospital visits
· Prioritize patients for in-hospital visits.
· Postpone all elective non-urgent pain procedures.
· Use telemedicine to its full capacity for triaging priority patients
· Consider telemedicine over face to face interaction, whenever possible.
·Adhere to the national, local and institutional legal and ethical guidelines for practice of telemedicine.
Prescribing Opioids:
·Don't change the on-going opioid treatment regimen without significant change in pain intensity or functional status.
· Use real time visual modalities of telemedicine, whenever is feasible to assess the compliance, monitoring of on-going opioid therapy and to assess the need to initiate opioids.
· Always document in the medical records during every visits (telemedicine and in-hospitals visits)
· Follow national, local or institutional policies for providing e-prescriptions of opioids.
· Any patient, who needs initiation of opioid therapy or change from one opioid to another, needs to have an in-hospital visit.
·For institutional dispensing of opioids, identify a key caregiver during teleconsultation and ask him to come to centre to collect the drugs. If the pain is stable, dispense at least drugs for 30 – 60 days.
· Any patients on opioids for cancer pain should be provided with an institutional emergency 24*7 helpline number.
·Educate patients and caregivers about potential side effects of opioids, including risk of infection; educate them for maintenance of hygiene and infection control strategies.
· Be extra careful for patients with fentanyl patch. If a patient develops fever, the patch should be removed and family should contact the emergency helpline number immediately.
Prescribing NSAIDS:
· Should be prescribed and continued in adherence with WHO pain ladder.
· Educate the patient to report immediately over emergency telephone helpline number if there is new onset fever or myalgia.
Prescribing steroids:
· Continuing or starting new steroid therapy for pain management in cancer patient should be individualized strategy based on benefits and risk of infection.
· Use dexamethasone or betamethasone whenever needed.
· Avoid use of steroids as adjuvants in neurolytic blocks and neuraxial administration.
Procedural considerations:
· Take up only urgent cases for pain intervention.
· All patients should be screened for symptoms and epidemiological link of COVID 19 before procedure.
· Follow local or institutional guidelines for RT-PCR testing of COVID 19 before the procedure.
· For COVID negative or low risk cases, perform in non covid area and for COVID positive or high risk cases perform the procedure at a designated COVID area of hospital.
· Use proper and adequate personal protective equipment (PPE).
· Minimize movement of staffs in the room.
· Use disposable items; don't bring trolley into the room.
· Cover all the reusable equipment in plastic covers.
· If general anaesthesia is required, take all precautions to minimize aerosolization.
Plan of palliative radiotherapy :
· Use single fraction (8Gy,1#) palliative radiotherapy, whenever needed for bony pain.
Psychosocial support:
· Use telemedicine and online platforms to provide access to peer support group.
· Involve patients on online cognitive behavioural therapy sessions from experts.
· Maintain physical distance instead of a social distance with family members.
· Refrain from panic creating social media and news.

Therapeutic concerns and adaptation strategies for managing cancer pain

As managing pain is a priority in cancer patients, we need to adapt to some strategies based on the concerns involving biophysiological interactions of analgesics and challenges imposed on systems due to pandemic. The basic principle for these strategies are minimizing the risk of infection in patients without affecting the pain management to its minimum. A summary of recommendations for adaptation strategies are presented in Table 1. The major strategies are described below:

1. Prioritization of patients for in hospital visits

Decreasing the daily footfalls of patients and caregivers in hospitals for routine follow up during the on-going pandemic is important. This mandates to create

Table 2. The High Priority Patients with Cancer Pain for Urgent in-hospital Visit During Pandemic

Acute Pain	Acute on Chronic Pain	Chronic Pain
1. Severe (NRS>7/10) pain arising from treatment of anticancer treatments : · Grade 3 and 4 oral mucositis.*1 · Chemotherapy induced peripheral neuropathy WHO*2 grade 3 or 4 ·Acute post chemotherapy enterocolitis. ·Acute radiation induced bone pain. · Radiation induced plexopathies. · Radiation induced proctitis. · Acute pain flare after hormonal therapy · Extravasation of cytotoxic agents. 2. Severe (NRS>7/10) pain arising from interventions : · Acute severe postoperative pain. · Biopsy · Thoracocentesis. · Catheter insertion.	1. Severe breakthrough pain (NRS>7/10), not subsided by oral rescue doses. 2. Severe (NRS>7/10) pain related to tumour: · Impending vertebral collapse. · Pathological fracture. · Hollow viscus perforation. · Malignant bowel obstruction. · Large malignant ascites. · Raised intracranial tension in brain metastasis. · Haemorrhage, infection in tumour. · Invasion of tumour into bone. 3. Severe (NRS>7/10) pain related to analgesics: Opioid induced hyperalgesia.	1. New onset of opioid therapy. 2. Change over from one opioid to another. 3. Refilling of opioids. (In hospital visit at least by care giver after real time teleconsultation). 4. Patients with side effects of opioids, e.g. respiratory depression, sedation, severe nausea and vomiting not controlled by oral medications, severe constipation not relieved by usual drugs etc. 5. Patients on fentanyl patch, having fever. 6. Patients requiring urgent pain interventions: · Intrathecal pump (ITP) failure, displaced or disconnection causing inadequate delivery. · ITP refill with medications and before expiry of battery life to prevent withdrawal symptoms · Infection of the implants.

*1, Toxicity grading of oral mucositis (OM) according to World Health Organization (WHO) and National Cancer Institute Common Toxicity Criteria (NCI-CTC) criteria [83]; *2 Oncoprof. WHO toxicity scale. 2009 [84].

Table 3. Procedural Precautions and Strategies

COVID 19 negative and low risk cases	COVID 19 positive and high risk cases:
1. Patient to be managed at a clean non covid area.	1. All patients to be called at designated COVID areas.
2. Patient should enter wearing a surgical mask.	2. All staff should wear full personal protective equipment (PPE).
3. Minimize the staff numbers in the room to minimum. 4. All staffs should wear impervious gown, well fitted N95 mask, head cap, shoe cover, face shield and sterile gloves. 5. Arrange all the drugs and equipment beforehand; bring them to the procedure room in a clean plastic bag. 6. Cover the ultrasound probe with plastics to avoid contamination.	3. Airway management during anaesthesia should be done by most experienced person with rapid sequence intubation. Bag mask ventilation should be avoided. The intubation should be performed under a customized intubation box or plastic cover. Always use two viral filters, e.g. one at patient end and one at expiratory limb of ventilator [73-74]
7. Doff and Perform hand hygiene properly at the end of procedure.	4. Rest precautions are as same as for low risk cases.

a triaging method for choosing the high priority patients for managing cancer pain in the hospital setting. The high priority patients with cancer pain can be categorized as acute pain syndromes, chronic pain syndromes and acute on chronic pain syndromes (Table 2). Some of the examples of such high priority patients for cancer pain management are as follows, but not limited to:

• Acute exacerbation of chronic pain (Numeric rating scale [NRS]>7/10), not controlled by oral therapy.
• Patients with impending spinal cord compression.
• New onset pathological fracture.
• Severe Pain following an oncological treatment.
• Patients having side effect of the pain therapies, e.g.: overdose of opioids.
• An intrathecal pump disconnection or displaced.
• An infected pain device implant.

A screening method should be established for the patients before they visit the hospital for pain management. Telemedicine is a potential modality of screening patients with chronic pain for priority service. The telemedicine service has regained its popularity during pandemic as it does allow face to face interaction with patients over a video consultation with good patient acceptability [61].This can aid to physically examine the patients, checking the compliance by counting drug strips [62] identifying any reactions or side effects to the therapies and consulting with primary physicians [63] to take a shared decision. Many countries, e.g. Canada,

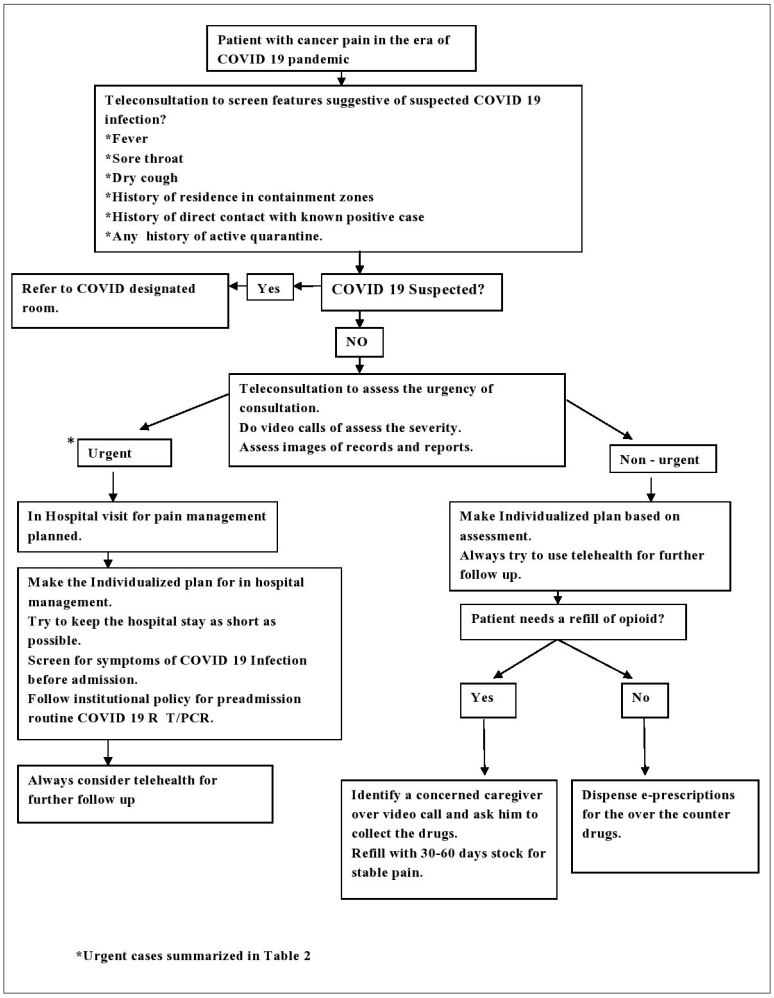

Figure 3. Integrated Strategy of Prioritization Patients with Cancer Pain for in Hospital Visits During COVID-19 Pandemic

UK, US has waived off the restrictions on previously imposed restrictions on use of telemedicine. Some of the countries, e.g. India [64] has allowed registered medical practitioners to use telemedicine mainly addressing the current pandemic situation and may be amended from time to time in future. Thus, the practitioners need to be updated about such regulations and license required for practicing pain management and prescribing drugs over telemedicine. Moreover individualized assessment for urgency and treatment plan should be made for each patient. Figure 3 describes an integrated strategy of implementing telemedicine service for prioritization of patients and prescribing medications.

2. Prescription strategies of analgesics

The analgesics prescription should be majorly based on conventional WHO pain ladder. Following drugs need careful consideration and some guiding principles for prescription:

A. Opioid Prescription strategies:

Opioids prescriptions need special consideration as opioids potentially supress the immune system [38]. Though there is still lack of good randomized clinical trials [65], many literature suggests that opioids cause an unfavourable modulation of immune system and increase severity of respiratory infection. Moreover, fever is one of the common symptoms in cancer patients. Fentanyl absorption from transdermal patch increases in such patients [66] precipitating the respiratory depression.

Another major concern for prescribing opioids is legal barriers. In most of the countries prescriptions of opioids are regulated by strict laws with vigorous punishment. As for example, In India the prescription of opioids is regulated by the amendments of the Narcotic Drugs and Psychotropic Substances (NDPS) Act, 2014 [67]. The restrictions on e-prescriptions of opioids are still on, even after the recent amendment of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulation, 2002 by the Board of Governors (BoG) along with NITI Aayog on 25th March, 2020 [64]. A recent petition has been filed by the Indian academy of palliative care (IAPC) at the Board of Governors (BOG) of medical council of India (MCI). It seeks relaxation on refilling and changeover from one opioids to another over teleconsultation. But, the decision on this petition is still pending. Thus we recommend not providing e-prescriptions for opioids in India. But, telemedicine with real time video consultation should be used to maximum capacity to evaluate the pain, checking adherence to

opioids therapy and monitoring side effects. Any initiation or changing one opioid to another needs an in-person visit. For prescription and dispensing of opioids, a responsible caregiver should be identified during teleconsultation and sent to hospital to collect it, if the patient cannot come to the clinic. As, opioids are key medications for managing moderate to severe cancer pain, it is important to balance the risk of infection and desired analgesics effect of opioids. Thus, we suggest the following principles to be followed during pandemic to prescribe opioids in cancer patients for pain management:

a. Don't change the on-going opioid treatment regimen without any documented significant change in pain intensity or functional status.

b. Use real time visual modalities of telemedicine, whenever is feasible to assess the pain and document it in every follow up visits.

c. Use real time visual modalities of telemedicine, whenever feasible, to assess the compliance to opioids therapy by pill counts. Always cross check, document in the medical records.

d. Many countries do not allow e-prescriptions of opioids yet. Thus, providing prescriptions and dispensing of opioids should be only in person in such cases. Identify a key caregiver during teleconsultation over video calls and ask him to come to centre to collect the drugs. If the pain is stable, dispense at least drugs for 30 – 60 days to decrease the need of travel. Any initiation or changing one opioid to another needs an in-person visit.

e. Always identify a primary caregiver and educate them along with patient himself about potential side effects of opioids. Provide an emergency helpline number to assist and guide them in case of suspicion of opioid overdose.

f. Inform and educate patients and family members about the risk of infection in patients with opioid therapies, especially with high dose of long term opioid therapy. Educate them about infection control strategies, e.g. hand hygiene, coughing or sneezing hygiene, use of masks, restricted entry of visitors etc.

g. Be extra careful for patients with fentanyl patch. Patients should be educated about risk of overdose in case they have fever. If a patient develops fever, the patch should be removed. An emergency helpline number should be available with patient to help them in such situation. Such patients should be considered as a high priority patients for in hospital management with isolation facility.

B. Anti-inflammatory drugs prescription strategies:

There are some evidences, as already described earlier, that suggest that NSAIDS may aggravate the complications in a COVID-19 patient. But the evidence is not direct and concrete. Thus NSAIDS should be continued for a patient whenever needed. Although, educating patients about some warning signs of COVID-19 infection is important for them. Always provide with institutional emergency helpline number for such patients. The following major principles should be followed during the pandemic:

a. Continue the anti-inflammatory agents for all the patients who were previously on it.

b. Can start the drug in new patients if required for control of pain, especially patients with somatic or bony involvement.

c. Educate the patient to report immediately over emergency telephone helpline number if there is new onset fever or myalgia.

C. Steroids prescription strategies:

Steroids are considered as useful adjuvant in many cancer pain syndromes. But, there is risk and controversy regarding use of steroids in patients during in the pandemic, as it can lead to altered immune response [68]. Thus, following principles should be followed while using steroids for cancer pain management:

a. Continuing or starting new steroid therapy for pain management in cancer patient should be individualized strategy. The risk of infection and benefit in pain management should be weighed in case to case basis. If there is any doubt regarding this, one should take opinion from an infectious disease expert.

b. Whenever steroid needs to be used, use dexamethasone or betamethasone, as they cause short term immunosuppression as compared to methyl prednisolone [69].

c. Avoid use of steroids as adjuvants in neurolytic blocks and neuraxial administration, as evidence suggests them not to be safe [70].

3. Strategies for interventional procedures for cancer pain:

Interventional pain procedures are now an integral part of cancer pain management [71]. Different interventions, e.g. intrathecal pump placement with continuous neuraxial drug delivery, neuromodulation, neurolytic blocks etc have shown a better quality of life in terminal cancer patients. But, pain procedures are known to cause several complications, including serious life threatening infections [71-72]. Thus two main adaptation strategies should be adopted for pain intervention procedures in cancer patients during this pandemic:

a. Choose only "urgent" cases as eligible for interventional procedures.

b. Follow procedural considerations for strict infection control.

a. Choosing "urgent" cases for pain intervention:

Though modification of WHO ladder suggests an early integration of interventional procedures for cancer pain, the scientific evidences are limited and not robust. Thus an individualized approach should be considered for patients requiring interventional pain procedures. Only cases where benefits clearly outweigh the risks should be considered for eligibility. All new insertion of implants should be avoided. Pain interventions often need hospital admission for the patient and even administration of anaesthesia for it. During a pandemic, when decreasing footfalls of patients at hospital is a priority, we need to be very careful to choose only those patients who require pain interventions urgently. Examples of such "urgent" conditions may include, but not limited to the following: [73]

• Intrathecal pump (ITP) failure, displaced or disconnection causing inadequate delivery.

• ITP refill with medications and before expiry of battery life to prevent withdrawal symptoms

• Infection of the implants.

b. Procedural considerations and strategies [74].

Any intervention needs special precautions during a pandemic regarding infection control strategy. At our centre, All urgent cases of intervention undergo a screening for COVID -19 (RT-PCR) before the procedure, as per our institutional protocol. We suggest following local or institutional protocol regarding preprocedure testing. History taking and examination should take place over video consultation before calling every patient to the hospital. History taking should rule out features suggestive of a suspected case of COVID-19, e.g. fever, dry cough, history of residence in containment zones, history of direct contact with known positive case or any history of active quarantine. Usually the procedures are less aerosol generating, they are considered as low risk cases. But, the procedures, if needs an administration of anaesthesia, it should be considered as highly aerosol generating and high risk procedures [75-76]. The strategies are summarized in Table 3.

4. Considerations for palliative radiotherapy (RT):

Palliative radiotherapy is an useful adjuvant modality for managing resistant bony pain due to metastatic cancer. Providing radiotherapy needs in hospital visit by patients. Moreover acute side effects of palliative radiotherapy may be seen after radiotherapy up to 4-6 weeks [31]. Thus, it is the need of the hour to decrease the dose and duration of palliative radiotherapy. The European Study Group of Bone Metastases (GEMO) has already published their recommendations for palliative radiotherapy in painful bony metastasis [77]. The following principles should be followed in view of the current pandemic:

a. Palliative radiotherapy should be considered pain due to bony metastases which is not responsive to strong opioids, patients with acute intolerance to opioids, with impending spinal cord compression.

b. Use single fraction radiotherapy (8Gy/1#) instead of conventional fractionated treatment (20GY, 5#) [77].

c. If a repeat session is required, wait for at least 4 weeks [78]

d.In metastatic spinal cord compression, routine use of high dose steroids during radiotherapy is poorly supported by evidence in literatures. Thus we suggest using a short course of corticosteroids (Dexamethasone 16 mg daily) only if there is high chance of acute inflammatory oedema after radiotherapy [77]. A suspicion of COVID-19 infection needs to be ruled out in all such patients who will be considered for corticosteroids.

5. Providing holistic care for pain:

Cancer pain can be multifactorial and needs multimodal approach of management. Dame Cicely Saunders coined the term “total pain” for describing multidimensional domains of pain [79]. The same concept has been adopted for managing cancer pain time and again. et al. showed that managing psychological distress helps to manage cancer pain better and improves overall quality of life. Social distancing and quarantine in the era of pandemic has tremendous impact on psychological distress of the patients [80]. Social stigma and restrictions in mobility tends to cause barriers for the patients to access the social support groups and trained psychologists. Telemedicine can be an effective alternative to provide this psychological support to them. Feasibility and viability of an online system for managing chronic pain with multidisciplinary approach has been already established [81]. As compared to a face to face session, online individualized cognitive behavioural therapies for cancer patients can be really helpful and effective to deal with the psychological distress [82]. Different types of nonpharmacological interventions that can be provided through an online platform are providing mindfulness therapies, interactive peer support groups, expert counselling for grief and bereavement, physical rehabilitation training and cognitive therapies.

In conclusion, management of cancer pain is a priority service during pandemic for health care providers due to its physical and ethical considerations. The possible biophysiological considerations of different analgesics with COVID 19 infection should be kept in mind. The strategies adopted for safe and effective management of cancer pain includes prioritization of patients for in hospital visits and urgent interventions, special precautions for prescribing high dose of opioids, steroids and NSAIDS, modification in dose of palliative radiotherapy and using telehealth whenever feasible for screening, triaging, managing therapies and providing psycho-social support. Further high quality clinical trials and an international collaborative consensus guideline for managing cancer pain is the need of hour and highly recommended.

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REVIEW

Tally Education in Covid-19 Era: Impact on Health, Cancer Care and Education Sectors

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Abstract

The present paper will highlight the impact of COVID-19 on different sectors like cancer care and cancer patient's management and on the education system. With this pandemic, almost all the sectors have been affected badly but the major impact is visible on health care and education system because both these sectors demands face-to-face interactions as far as traditional approach is concerned. However, the good side of this event is several artificial intelligence-based methods have been evolved to minimize the impact of this pandemic on health care, research and education sector. This led to the evolution and revival of modern methods like telemedicine, video conferencing etc so that the motive of social distancing shall be fulfilled to avoid community spread of this deleterious infection. Different web platforms are being used for this purpose to name a few Google Meet, Zoom, Microsoft teams, WebEx and so forth. The ultimate goals however remain the same in both these sectors which is to meet the demand and supply, to provide assistance and to resolve the queries virtually without carrying out physical interactions.

Keywords: COVID-19- Telemedicine- cancer care- immunity- oncological societies

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Introduction

The coronaviruses which are human and animal pathogens marked the disastrous end of 2019 and sad beginning of 2020. The spread of this virus was initiated from Wuhan, a city in the Hubei Province of China. From epidemic this very soon changed to pandemic. This led to epidemic throughout the country and then followed by increased number of infected people across the globe [1-2]. The World Health Organization does the nomenclature of the disease as COVID-19 which stands for Coronavirus Disease 2019, in the month February 2020. This virus causes severe acute respiratory syndrome. Because of such a widespread of the disease global lockdowns happened around the globe and these events weaken down the health care system. Theses global cut offs presented several medical challenges globally in the health care management and especially in cancer care and management of cancer patients. The scenario of communication and interaction is now changing worldwide. COVID-19 era is actually redefining the policies and guidelines for governments, economic sectors, higher education sector, healthcare sector and research. Since then several guidelines have been issued by health ministries & oncological societies for proper management of cancer patients in this pandemic, COVID-19's petrifying and dangerous effect has shaken the world to its core [3-4-5]. Moreover, as a measure to lower the spread of the COVID-19 pandemic, most governments around the world temporarily closed educational institutions so that the community interaction chances shall be minimized. In India too, the government as a part of the nationwide lockdown has closed majority of the private hospitals, all educational institutions, as a consequence of which, medical practitioners, oncologists and majority hospitals restricted the visiting hours and visitors & learners ranging from school going children to postgraduate students, are affected. It has great impact on the thinking of almost all individuals worldwide and for

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sure this radical change will be visible for longer period in the society [1-2]. To count the biggest transformation then that will be the one introduced in the health care system, research activities & higher education sector because of COVID-19. In this the science of artificial intelligence & deep learning models will play a very significant and crucial role. These branches of science will help in creating and customizing new methodologies for learning and imparting education & information online. However, the implementation of these learning methods will come up with some challenges and will also demand innovations at regular intervals of time to overcome the shortcomings or ills generated during the course of administration. The post COVID-19 era, will not just led to antiquation of conventional way, however, will also provide blending of modern methods for patient's welfare and proper management; and also, methods of learning having both online and classroom teaching, as per the demand of the subject and curriculum. Though this combination will present some challenges as well in front of the health care & education sector like how to match the demand of internet infrastructure so that hazzle free interactions and online classrooms shall be conducted [1-2-6-7].

Challenges in Cancer patient's management in COVID-19 era

Cancer patients have higher risk of developing severe consequences due to COVID-19. The interaction may lead the cancer patient's admission to ICU (intensive care unit) which may require invasive ventilation or death of the cancer patient may occur as compared with other disease patients. It did not establish a definitive increase in incidence of COVID-19 infection. The different challenges faced by the oncologist, cancer patients and managements units during this pandemic includes inadequate infrastructure; lack of management and skilled management unit and cancer care professionals [2-3-4-5]. This situation also disclosed the serious glitches in the supply-chain in cancer care across the world which resulted in compromised state regarding the safety and care of cancer patients. The cancer patient's management proved to be little more complexed during this pandemic because of lower immunity of the patients these are at higher risk of getting the infection. Another major impact of COVID-19 is on the translational research in the field of cancer which will lead to delay in the implementation of research data in cancer care advancement and critical care. The main objectives of the recommendations given by different health ministries and oncological societies is to control the adverse effects of COVID-19 pandemic on diagnosis, treatment and management of different forms of cancer across the world. The guidelines issued also suggested that some serious and realistic actions are to be taken to overcoming the challenges of treating cancer patients and to ensure their well-being in such a pandemic situation. Furthermore, these recommendations will guide the patients to decrease hospital time and interaction with medical practitioners. This era has revived the base of telemedicine in cancer care to provide video or telephonic consultation to cancer patients to be précised the telecommunication will support pre-treatment and follow-up meetings and appointments. The main motive of such regulations is to ensure telemedicine approach to decrease personal interactions by allowing extended electronic prescriptions so that repeated home-based oral cancer treatment shall be followed without the need for additional appointments during the pandemic [6-7-8-9-10].

Rise of Digital Technology in cancer care and education sectors

The most crucial challenge in the beginning of this pandemic was to deliver required care to cancer patients due to risks of severe outcomes and even death from combination of cancer and serious complications from COVID-19 as these groups of individuals are already immunocompromised. Because of which uncountable number of cancer patients suffered across the globe as the hospitals were either delaying or cancelling their surgeries and other procedures, like chemotherapy and radiation therapy. All this happened because of insufficient supplies of personal protective equipment (PPE) for health care providers, hospital capacities like ICUs were limited. Furthermore, seroprevalence data and lack of point-of-care testing also complicated the process [2-4-11-12]. Similarly, education sector faced number of problems since it too demands face to face interactions. Therefore, in health care institute, hospitals, educational institutes; data processing approaches, and online education technologies were required to operate in tandem due to the rapid adoption of digital technology caused by this lockdown. A significant number of these institutes are thinking about this as a perfect chance to analyse and send innovation to ensure that the training conveyance is conceivable and important. The pandemic has had a heavy impact on the shift from a one-to-one talk-based model to a digital one. This gap in the expression of instructions is putting pressure on the policymakers to find ways on how to have an e-learning arrangement that is commitment driven and would guarantee comprehensive learning. Any kind of change that is disruptive is also probable to deliver with it a few new opportunities that facilitate to convert the health care and higher education system globally and mainly in India which is making plans to convey the health care & education system into a whole new level. To elaborate, post Covid-19 represents a chance to transform these sectors. Therefore, these sectors should take advantage of this opportunity to transform themselves. Introduction and revival of telemedicine, video conferencing in health care, curriculum design, collaborations, development of skills, and involvement of the staff — all should focus on internationalizing and globalization for better and effective outputs [1-2-7-10].

Some of the key areas of opportunity are as follows

The rise in Blended Learning

Health care and education sectors will move to a new model of realizing where both up close and

personal conveyance alongside online models will turn into a standard. Additionally, this will require Medical practitioner/Lecturers to turn out to be innovatively further developed and experience some preparation to carry themselves to another level. In the area of telemedicine, patient's follow-up, curriculum development and pedagogy, new ways of assessing outcomes will have to be adopted which opens immense opportunities for a major transformation.

Learning management

For those companies that have been developing and strengthening learning management systems to be used so that great opportunity will be opened.

Improvement in Learning Material

This is an extraordinary open door for sectors to begin improving the nature of the learning material which is utilized in instructing and learning processes.

Since mixed learning will be the new arrangement of realizing there will be a push to discover better approaches to plan and convey content because of the way that utilization of learning the management system will get more openness and straightforwardness in health care and academics.

The National cancer grid took the rigorous initiative to share best practices and guidelines for cancer treatment during COVID-19 pandemic by organizing learning and informative webinars. They also established the open electronic-communication channels and a process for shared decision making, despite circumstances that preclude face-to-face meetings. This surely will be led to robust health technology assessment program, an essential tool in a country where public health care expenditures are low [1-2-7-10].

Impact on Education system in India

The UNESCO report estimates that more than 290 million students across 22 countries will suffer from coronavirus pandemic. UNESCO estimates that about 32 crores students are affected in India, including those in schools and colleges. Although the crisis is devastating, it makes our education system technologically advanced, but despite this, students and faculty have to make bigger adjustments because the learning method has always been physical. Many of them are not well equipped with technology tools to avail of remote learning. The traditional education system in India follows one-to-one based physical teaching, while a decade ago the advent of audio-visual aids was introduced in classrooms. Renowned Indian universities such as the University of Delhi also offer their students, online classes. But most of India's higher education institutions do not possess these high-end configurations. The presence of such an inconsistency, students are forced to be in a situation to face the impact which in turn would affect their performance for the whole academic year. Some bad Impacts of Corona Virus on Education System are:

Cross-border Movement of Students

Universities in many countries such as Australia, UK, Canada, and New Zealand are surprisingly dependent on the motion of students from China and India. So, its miles very clear that the cross-border movement will take the beating for the following 2-3 years and in the end can be leading to a fundamental economic risk for universities.

Passive Learning

As we realize that there is this unexpected move to web-based learning without appropriate arranging, which intensely influences nations like India where the spine for web-based learning was not prepared, and educational program was not intended for such an arrangement. Likewise, web-based learning could be a dull arrangement of instructing as it is making another arrangement of uninvolved students which can present new difficulties.

Unprepared Teachers/Lecturers

Online teaching is a very unique type of technique and now, not all instructors are suitable at it or not all of them are equipped for this type of unexpected change from face to face learning to an online one. Potential outcomes are there that in such circumstances, learning results may not be accomplished and it might be just bringing a distraction to the students [1-9].

Gearing up of diversified and interdisciplinary collaboration in post COVID-19 era

This whole situation has illustrated that we are globally interconnected and when it is so then it is significant to understand the inter-relatedness in diversified and interdisciplinary work across boundaries and work in a globally collaborative way. The interdisciplinary collaborations will be beneficial for the professionals, organizations and to the public, private & government systems. These collaborative initiatives will strengthen education and research systems, stakeholder's satisfaction, acceptance of new implementations and improved outcomes. This will gear up diversified and interdisciplinary collaboration in COVID-19 and post COVID-19 era will also integrate "the input-processes-output approach". This concept will help to deepen theoretical understanding and will also resolve the challenges in analysing the current state of knowledge. It provided the rationale for this systematic review. The invasion of COVID-19 has a tremendous impact on different strata of the society in several ways and has shown the importance and benefits of multi-sectorial collaborations. And will prove the benefits of sharing of expertise across different groups world-wide to come up with enhanced and effective outputs. The policy-makers will now focus on interprofessional collaborations which will be based on the infrastructure of the educational landscape. The main focus of these collaborations will be centralization of information gathered through research, maintaining the time lines for effectiveness, new safety regulations to be published (mandatory use of personal protective equipment; PPE) and maintaining enhanced

efficiency and equity. These collaborations will enhance synergy between digital and in-person training modalities to ensure that critical outcome of research and education shall be communicated across world. These collaborations will allow integration of diversified and interdisciplinary approach into the routine of research and education and will ensure highest-yield activity. Both resilience and adaptability will induce and enhance interdisciplinary collaborations in post COVID-19 era. This era will give more importance to "one health concept", which is define by WHO as an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes [10-11-12-13-14].

New methods of diagnosis & prognosis in cancer care and assessment and evaluation in education sector (service and technology combination)

This era has given new horizons to the combination of service and technology. Several innovative methods have been explored for assessment and evaluation related to different domains including cancer care and education sector. Though technology has always influenced these two sectors majorly, however COVID-19 situation has redefined the different intersects where technology shall be implemented during process like diagnosis and prognosis in cancer care; and assessment and evaluation in education sector. This new era has marked the beginning of exploration of untouched spheres of technology. It is much about technology reaching to people (cancer patients and students) in the most effective and friendly ways with better outcomes [1-2-3-4-5]. These implications are procedures/processes accessible from distant locations, equally appropriate by incorporating vivid simulations of real-world situations. The new ways invented during this era are more flexible, responsive and contextual; and will be followed for next several decades. This has evolved next generation of service and technology combination through better incorporation and management of timing, accessibility, pathways, feedbacks and item types as compared to traditional methods. Incorporation of more and more computing and telecommunications devices has a major lay down in this era. This will be much about digital literacy and its implementation. These new methods will be combination of both synchronous and asynchronous. The main purpose of these implementations is to minimize personal or face-to-face contact, and increase virtual interactions through telephonic assistance or video consultations, particularly for pre-treatment meetings and follow-up appointments in cancer care. Both these methods have their own advantages & disadvantages as well. But the motive of both these methods on education sector is to impart required and necessary information through incorporation of different digital platforms [6-7-8-9]. Online instruction is led in two different ways. The first is using recorded information, which, when opened out to open, are alluded to as Massive Open Online Course (MOOCs). The subsequent one is utilizing live online directed as online classes, or zoom meetings [10-11-12-13-14].

In conclusion, COVID-19 is a global threat which is affecting the lives worldwide. It is caused by novel Corona virus called SARS-COV-2. At present there is no possible treatment for covid-19. However, the chances of infection can be minimized by boosting immunity against virus. This pandemic has not only affected the lifestyles but also the economy of the countries across the globe, the health care sector and the education sector. It has cause global socio-economic depression. But out of all the negative effect of coronavirus it has some positive sides as it contributed majorly to the digitalization or artificial intelligence. Health care sector is now switching to telemedicine concept in cases where of chronical diseases treatment like cancer where it is known that the patient's immunity is already compromised and therefore any kind of public exposure can be hazardous. Similarly, education sector has evolved a lot by adopting to artificial intelligence: synchronous and asynchronous methods of teaching. Globalization in field of health care and education sectors is the demand of this era. Collaborative works in field of research, health care and education will be more acceptable in this era.

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REVIEW

Challenges Encountered in Cancer Care and Management During Covid-19 in South Asian Countries

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Abstract

During the COVID-19, the cancer care is one of the most effected fields. The cancer care is either delayed or discontinued during the pandemic because of which cancer patients had to face resource constrain. Limited resources availability during this pandemic led to delay in the cancer diagnosis, undetected/ untreated cases and worse prognosis. The scenario of cancer care is even worse where the south Asian countries including India and Pakistan are considered due to unavailability of experts and adequate resources. Moreover, due to compromised immunity, the cancer patients are advised to restrict the number of visits to their Oncologist. Multipronged strategy to be included in different spheres of cancer treatment and cancer care. The ultimate motto of which is to ensure the well-being of cancer patients. The south Asian countries are framing different recommendations and guidelines to ensure the management of cancer patients through virtual/artificial intelligence modes, so that it shall promote contact less care and management of cancer patients in these countries. Since the beginning of Corona pandemic cancer care and research has been side lined all across the globe and in India & Pakistan as well. This article discusses about effect of SARS-CoV-2 on cancer treatment and nursing in these countries. The strategies for cancer research have also been changed now to cancer care. Urgent need is there to find-out causes of delay in treatment and diagnosis on different stages of cancer. There is a need to minimise the obstacles if the pandemic continues over the coming months.

Keywords: Cancer care- South Asia- India- Pakistan- COVID-19

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Introduction

COVID-19 a pandemic that came as an infectious and contagious disease caused by recently found virus SARS-CoV-2 or Corona virus originated in Wuhan, China on December 2019 [1]. Breaking all the records in Wuhan, soon it spread to the entire world effecting drastically the most developed and medically advanced countries like Italy and United States [2]. The spread of virus from China soon turned into an outbreak causing deaths with respiratory and multiple organ failures worldwide especially seen in immunosuppressed individuals to an extent that WHO had to declare it as an emergency. It declared and advisory stating that old people (above 60 years), kids (below 10 years), diabetic individuals, individuals with breathing troubles and Cancer patients should stay at home in quarantine to prevent themselves from COVID attack [3-4]. From studies conducted on several patients it was reported in Journal of Cancer Discovery in June 2020 that the patients with cancer are more prone to critical illness & die than the infected general population [5]. According to the various cohort studies conducted in a hospital in Wuhan, China from the period of December 2019 till June 2020 it was

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analysed that overall cancer patients admitted during this period, 79% were COVID positive in which 39% died in Intensive care unit while during the same period the general population of admitted to the same hospital was 37% COVID positive out of which 8% died, drawing the hypothesis that cancer patients are more vulnerable to the disease [6].

It was also observed through these cohort studies that the rate of fatality in case of COVID-19 was more due to multiple organ dysfunction than acute respiratory failure despite of the fact that it belongs to the family of SARS virus. This led to the explanation that this virus seriously affected the individuals with weak immunity like in Cancer patients that are undergoing chemotherapy and harmful medications. Such patients on attack with this virus developed multiple organ dysfunction more quickly than cancer patients who were not undergoing any chemotherapy [7].

Among the cancer patients it was found that the patients suffering from lung cancer, hematologic cancer and metastatic cancer stage IV were more prone to fatality due to COVID than nonmetastatic patients [8-9] and had more serious conditions. In addition to that the patients who had in past cancer surgery were also more prone to complexities of COVID to an extent of reversal of cancer or higher death rates [10].

The researchers and medical expert however do not conclude that COVID can cause fatality only to Cancer patients. There are several other factors that also came into light during these cohort studies. It was found that the patients suffering from cancer that died due to COVID were also older in age and some had history of smoking and breathing problems apart from going through chemotherapy [11]. One thing common all the fatal cases was poor or suppressed immune system in entire world including India.

Relation of Immune system with COVID

The ability of Virus to imitate the machinery of its host makes it difficult by our immune system or our defence system to locate any foreign particle especially if we have weak immune system. A healthy individual has strong force of defence cells inside the body that comprises of Major Histocompatibility Complex 1, Cytotoxic T cell, Helper T cells, Natural Killer cells, Macrophages etc. They all act as one big army that acts against any infection in our body. Virus usually release a protein called Viral interferons, that triggers the defence mechanism in the body. Once identified through MHC1 representation on infected cell, the cytotoxic cells release various enzymes to kill the virus by apoptosis. In case if Cytotoxic cells fail then macrophages and natural killer cells directly kill the infected cell with virus as a whole. So, it is seen that the machinery in our body is strong enough to combat any viral attack even if the virus mutates itself multiple times [12-13-14].

In cancer patients the tumour type, the stage of cancer, the age of patient, the type of therapy and supportive medications for cancer decide the rate of probability of contracting the viral infections. Such patients are immunocompromised because of antineoplastic therapy, chemotherapy (Steroid Supportive Medications) and immunosuppressive nature of cancer cells. Such cells alter the innate defence system of the body or may augment an untimely defence response like programme cell death/ apoptosis. Beside this usually the cancer patients that are old have other comorbidities and they have frequent visits to hospitals and nursing care, that further amplifies the complexities making them more prone to COVID attack [15]. So, it is clear from the above discussion that if one has strong immunity then chances of contracting COVID is less or if infected the severity of complication will be less and the recovery will be more.

Management and treatment of Cancer in India during COVID-19

India is a developing nation with upcoming medical facilities and updated medical care and to compare with medical giants like Italy, China, France and US is bizarre. Still India has put forward a strong front in combating the fatality of COVID-19. The ratio of fatality to the population of India effected is lower than the recovery ratio which was appreciated by WHO also [16]. The entire world is fighting the same catastrophe and experiencing the similar failures. For the first time entire world is united to fight the disaster with medical suggestions and practical approach taken by developed nation as the guiding light for health care workers and researchers worldwide [17]. But in India, the shoddy health care infrastructure, lack of good doctors and health care staff, inadequate knowledge and preparedness of pandemic and improper supply of resources has seriously compromised the patient care and safety of health workers. The hospitals being infected with COVID-19 has further worsen the situation. Even the Cancer Institute's scaled back after the reports received from China stated that COVID-19 is worse in Cancer patients [18]. With all these adversities and rationing in patient care the health workers in India designed their innate care delivery strategy especially for Cancer patients. The first strategy that was designed by two healthcare professionals of Tata Memorial hospital for cancer care delivery during COVID-19 as briefly mentioned below [19].

COVID-19 measures at Tata Memorial Centre (19)

1. Management

Formation of a committee known as COVID-19 task force & day by day briefings and formulating action plans.

2. Cancer Care

Avoiding complex medical procedures which requires various blood transfusions and delayed emergency care ward, Use of hypo-fractionated regimes at any point (eg, for breast, prostate, and lung cancers); arrangement of palliative radiotherapy in a uni-division/week by week course of action and Myelosuppressive systematic therapy should be decreased; moving on online specialists whenever possible; When extent of advantage is minimal the action should be postponed.

3. Directed- Patients

Checking camps to be made outside the cancer centre which will lessen patient visits, limitation in family members & companions in outpatient department and inpatient department, while routine follow ups should be changed to an online mode i.e. tele counsel.

4. Alerting Hospital

Foundation of set working systems for suspected cases/affirmed COVID-19 disease, body temperature facility and making of isolation area

5. Staff-Directed

Paid leave to be given to the individuals with high-risk (old aged staff, staff who is consuming immunosuppressive drugs, and pregnant staff); Shift changing of employees to guarantee an alternative in case of an occurrence of isolation and Provision to shift staff in emergency bus who are not able to arrive at work as a result of the transportation lockdown.

In India the hospitalisation is being given to most priority cases and mostly people if else healthy with no complications are advised self-isolation and quarantine for 14 days with basic medical and civic facilities from the state government. However, with cuts in hospitalisation and basic medical facilities the cancer patents are more prone to risk that otherwise is not life threatening at once. The cancer institutes and hospitals all over India are giving treatment first to the more curable cancer cases effected with COVID-19 that would benefit from the treatment over the non-curable ones that were as such in palliative care and the treatment would give only marginal effect. The decision helped in saving further the life of cancer patients with treatment for COVID-19 along with lifesaving cancer treatment. The decision seems harsh but in this pandemic time this is the only way to avoid regular cancer screenings and follow ups of cancer patients as to safeguard them from nosocomial infections related to infected hospitals and infected healthcare staff [20].

The establishment of National Cancer Grid that is the online web network of all the cancer centres in India was made by Tata Memorial Centre. This helped in sharing information and health protocols with the cancer specialist all over India through weekly webinars and webex. This is one of the most remarkable steps under Cancer Care strategy during COVID-19 by an institute. It has brought all the Cancer treatment and Preparedness for COVID-19 under one roof so that everywhere in India the cancer patients at this time are given similar lifesaving treatment [21].

The measures that are being taken by the health department of the State for safeguarding cancer patients is appreciable however, more important is preparedness of cancer patients by providing them complete knowledge of COVID-19 and its precautions. Informing them about basic hygiene, self-isolation, taking natural immunity boosters along with prescribed medicines and guiding them the new hospital care and visit only when it is very urgent [22]. To avoid increase of Coronavirus in Cancer patients the WHO guidelines i.e. isolate, test, treat and trace have to be adopted stringently for this Aarogya Setu app by Government is also very helpful. Through this app a Cancer patient can be aware of any active cases near his locality and the contaminant zones around his locality [23-24].

The Cancer centres through online follow ups with their patients are planning the treatment for them revolving around the strategies by Tata Memorial Centre [19], that has been broadly divided in categories: a) planned surgery- if required as per priority or can be delayed, b) undergoing immunotherapy, radiotherapy or chemotherapy- if necessary or can be delayed with specific life-saving cancer medications for time being, c) Stem cell transplantation- If not life threatening can be delayed and those with recent transplant should be kept in isolation to prevent them from COVID-19 infections, d) Antiviral therapy- this usually generated prophylactic response so yet it has to be confirmed that such therapy can be given to immunocompromised individuals, hence it should be avoided, e) antiviral medicines like Hydroxychloroquine, remdesivir7 etc are being given for treatment of COVID-19 but these drugs are not designed for COVID treatment so to try them on cancer patients is very risky and lastly (f) plasma therapy- The therapy involves transfusion of plasma cells carrying antibodies for COVID-19 from cured COVID-19 warrior to infected COVID-19 patient, thereby generating quick immune response in that patient and safeguarding him against this deadly virus [25]. Recently Delhi CM Arvind Kejriwal got approval for Plasma Therapy from ICMR to be conducted in hospitals named Rajeev Gandhi Super Speciality and LokNayak Jai Prakash for cancer patients after a successful clinical trial. It helped to moderate infected COVID-19 patients and is able to save their lives but in severe cases even this therapy is failing. So, Rajiv Gandhi Cancer Research Hospital is using this therapy on those cancer patients that are not very fatal and have chances to survive. These patients after therapy are given pulse oximeter to monitor their oxygen level daily [26].

So, it can be clearly stated that the effect of Cancer treatment during COVID-19 is shifted to Elective and Selective mode. The cancer centres as per WHO guidelines will isolate the patient first and if tested positive for COVID will be selected for life saving treatment and the surgery for the treatment of the cancer will be postponed by surgeon under elective surgery discipline that is depicted below [27]:

1. Examination of surgical need of cancer patient
2. Preparedness of Hospital with logistics and resource for the surgery
3. The consequences post-surgery to be mapped and aware to the patient
4. If delayed or postponed what risk it may impose to the patient
5. After analysis of above four points the final decision has to be taken.

This elective surgery discipline is very helpful in current scenario of cancer treatment in India as they are selected for cancer surgery only if they have two COVID-19 tests as negative after 72 hours. This step was taken because the cases of asymptomatic carriers is increasing in India in that case if inert COVID-19

patient undergoes surgery it may lead to severe critical complications and immune suppressions in individuals leading to their death. So, it is advisable till it is not necessary all the surgeries should be deferred [28].

The nature fury or a bio weapon, the source of COVID-19 is still untraceable but the magnitude of its occurrence and prevalence has made it listed in one of the most-deadly disease in the world. It's completely delusional as to when the COVID-19 outbreak will be over so every state is doing it preparedness post COVID times as well. Healthcare professionals are being given psychological help and all the possible support and resource so that they remain to be the COVID -heroes. The researchers, DRDO, CSIR, ICMR and all the research labs in India are trying hard to develop a drug or vaccine to eliminate this virus. The Government on other hand has increased testing laboratories, makeshift isolation centres and hospitals while stocking the antiviral and antimalarial drug in store [29]. The population of India are utilising their lockdown period in developing immunity and hygiene in themselves and guiding others around them to do the same. Probably on brighter version of life Post COVID-19 the cases in Cancer should reduce as people are trying to be more fit by doing yoga and exercises. They are more hygienic and eating healthy food and maintaining balanced diet that builds their immunity. So, hope for a brighter future for India post COVID-19 [30].

COVID-19 in Pakistan

Corona virus started spreading in Pakistan in Late February, 2020. Initially the number of cases remained low as China borders closed and check on the International flights were performed. Later at the end of February it started rising as 3000 religious pilgrimage returned from Iran and Saudi Arabia, with many are the carriers. Although the Government officials were strongly criticised for chaotic response but even then, most of the people were quarantined in sub-optimal conditions. Some countries including China also helped the Pakistan Government for coping the condition. At the end of March an increase was seen as most of the Pakistanis overseas from heavily infected countries travel back [31-32]. Initially the complete lockdown started since 13th of March. The social distancing measures were advised, large gathering of religious congregation was not prescribed. The month of March and April remained closed for all educational institutes, offices and business. Nowadays, country is in a state of partial lockdown and they are reluctant for a complete lockdown because of fear of economic havoc as 25% of the population are on daily wages. New facts and data of India also suggest this type of fear is most likely to be found in the developing Asian countries [32]. Stabilizing the economic loss in front of the COVID-19 is an inevitable task and Government like Pakistan which falls under low and middle income is already facing it.

Cancer care scenario in COVID era

Pakistan, is very populous with a head count of 220 million people. With each passing year the rise in the new cases of cancer also increased each year with 200,000 each year. There are very few centres in this country. The main hospital that is dealing with cancer sufferers are Shaukatt Khannum Memorial Cancer Hospital and their centres for research. These hospitals are also overburdened with the patients. Every year 45,000 new patients come to register for treatment in these research hospitals. Due to the limitation in the capacity only 10,000 new cases are able to be accepted while the remaining cases are declined. Pakistan also has more than 11% of the patient's which falls under category of child and sufferers are not only of Pakistan origin but also from neighbouring countries as Afghanistan [31-32-33-34].

Although the cancer hospitals accept the patients free of charge irrespective of the race and nationality. But there is a lack of availability and resources to deal with such larger population of people. The national budget and health structure if fragile and patchy. With the advent of corona pandemic, the situation seems to become more worse as the country already has limited ventilators of 4000 working ventilators for a population of about 220 million.

Balancing the risk of COVID 19 with economic crisis, and starvation, and this task is unavailing for low- and middle-income countries people. Cancer care is a complex, expensive, time consuming and it is becoming difficult now for the patients and their families. The care of cancer is a complex procedure, it involves expensive and time consuming and is difficult even at the best of times. Economic uncertainty, as well as obligations on the normal and ongoing clinical check-ups because the pandemic complexes the complication of cancer [31-32-33-34].

Cancer care is a prolonged, and expensive treatment. It is difficult for the patients and their families to cope with it in normal circumstances. At present due to economic uncertainties and restrictions on the travel worldwide and within the country the care and treatment of this disease become more difficult. At the second largest city Lahore we have just 200 beds in Shaukat Khanum Memorial Cancer hospital, although it is considered a large hospital by public sector standards. Although for COVID care there are 1,000 + bed hospitals in the city that have greater capacity to offer such care quarantine services. One of the major issues lacking in this country is ICU beds and ventilators. Shaukat Khanum Memorial Hospital devised a plan for increasing the number of ventilators from 11 to 15 by using available resources so that it reaches up to 50 ventilator beds. While normal inpatient beds have already converted to an ICU, to allow this expansion of beds [35-36].

The provincial Government is also supporting the cancer hospitals by giving the major equipment as primarily ventilators and cardiac monitors to monitor the cancer patients to operationalize the beds. Most of the hospitals are not taking the cancer patients most were not able to travel, in any case—and rapidly curtailed the visit of these patients for normal check-ups. The emergency cases including chemotherapy, radiation therapy is still continued. In addition to this a third inpatient unit has been opened for the patients having the coronavirus who are

not in that stage to need an ICU, or have just recovered from ICU. The Shaukat Khanum hospital has recently made a decision that any spare beds are going to be used by the patients of corona patients who are unable to pay for their treatment [35-36].

Molecular pathology labs have started providing services for COVID-19 patients testing as part of effort against the coronavirus. Radiology services and essential imaging services are continued for COVID patients. While all elective services and screening procedures like endoscopy has been stopped. There is a nationwide shortage of the protective equipment's for COVID they include surgical gloves, N95 masks/ filtering face piece particle mask. Some of the developed textile industries has taken a step and started manufacturing gowns and other protective clothing, and several local manufacturers are now able to produce manufactured gowns and personal protective clothing (PPE). Efforts of producing N95 masks are also commenced but there is a concern to whether this can be equally efficient in current pandemic situation [31-32-33-34-35-36].

Pakistan National Disaster Management Authority has given the task to buy the personal protective clothing and then distribute to the needy people. The demand of PPE although has been increased globally and there is a global shortage and enormous demand everywhere in the world. In Pakistan there is a culture of attendants to accompany along with the patients. Normally three to four patients accompany to each patient. Now there is a restriction on the coming of attendants with the patients. There is also the initial screening available for all the people entering the hospitals by checking the common COVID-19 symptoms including fever, cough and breathlessness. All those patients are referred in separate building outside the main hospital. Following further treatment such patients are advised to self-isolate until their results are available. Moreover, the triage centre for patients are also opened 24 hours and number of patients seeing per day is increasing. The separate facility in hospitals like Shaukat Khanum and other cancer hospitals has helped the patients to be divided on the basis of treatment and now are identified easily. Separate routes of entering for chemotherapy patients are now available as to protect the chemotherapy patients or the patients having the severe cancer progression can be protected. This is now helping and protecting the cancer patients as till date the rise of the corona patients is increased in Pakistan with 1000 patients per day. There is a need in various hospitals to designate the parts as patients with COVID infection (red) suspicious (yellow) and non COVID (green) thus the easy identification and care could be established [35-36]. Most of the cancer and other hospitals has established the virtual clinics for identifying and separating patients and normal individuals. Pakistan is a country with very good mobile networks so almost 90% of the people have the mobile coverage. Pakistan has the highest rate of mobile penetration in South Asia so consultations are also being carried out by using the WhatsApp calling systems. Although many patients have not the WhatsApp calling but their response is positive with the relief that they are in touch with the medical specialists. Prescriptions and advices are also sent by using the SMS and screenshots services. The main patients facing the problem is about the purchase of medications of cancer as well. The people are in the financial crisis and supply of drug also changed. The strategies for treating the cancer patients having corona virus has also been changed. There is a need for revising the protocols for treating any patient of cancer affected by corona. Most of the liver cancer patients has been asked to take medications like oral sorafenib for the ones who do not need the immediate visits [31-32-33-34-35-36].

Those patients who are on chemotherapy have to wait for a longer period of time than the normal routine or they may be treated with the additional cycles to cope with long waiting time. In Pakistan since the beginning of COVID-19 in March 2020 new patients admitted for cancer treatment has been reduced to one third. The patients already having the radiation treatment has been reduced to half. According to one report out of normal treatment where 800 elective surgical procedures has been carried out since lockdown condition the rate of that procedures goes down to 20 [35-36].

There is also a need for counselling sessions for the healthcare and support staff who are working in this situation. Although some support session for cancer patients has already been setup by using the telemedicine facility. Most of the cancer clinics and hospitals has seen the rapid drop of the clinical income which are derived from the diagnostics services and pathological collection. Some of the hospitals have also cut down the salary of the staff by 10%. Ranging from 25% reduction of highest paid and 5% reduction of lowest paid workers. New doctors and cancer professionals are also now hard to train and retained in resource limited environment. The patients with some associated reasons are only admitted based on variety of factors as age, availability of appropriate drugs, likelihood of having the complete cure etc. While most hospitals have already developed the system to accept the patients based on the severity of disease. To date Pakistan has 199K confirmed cases with 4000 deaths and 2729 critical patients. The cancer treatment and check-ups are now reduced which will affect the survival and prognosis of cancer patients. There is a need to keep going the normal check-up and facility availability to cancer patients so that they may not suffer from corona pandemic. Immediate strategies for care for cancer and corona effected patients need to be devised [31-32-33-34-35-36].

Challenges in the minds of people: Questions raised in people's mind due to fear

Patients have developed fear, a very dark fear due to COVID-19. If left unanswered these may cause anxiety in public and turn the situation in the worst. Therefore, it is important to address these questions.

"Is cancer or COVID-19 going to execute them?"

"What might be the smart solution for patients to do?

"Consulting doctors are saying they have to hold and sit tight for the treatment?"

"How might they save themselves?"

There is a big question in the minds of patients "What

if cancer increases, will all the past treatment they had will be effective?" "No one is able to tell anything even doctors are scared to treat cancer patients. This obviously portray stress and a decrease in patients to the hospitals.

In conclusion, care for cancer patients has been majorly hit all over the world. In India and Pakistan as well, cancer care is affected badly. The serious issues in these times of COVID is faced by Cancer patients because of their weak immune system as they are more prone to this Corona Virus disease which the world is facing. Mortality of cancer patients has increased as cancer treatment has been stopped and many hospitals has been totally converted to COVID Hospitals for treatment of Corona. Travel limitations was also imposed by the central and the state government of India which also reduced access to the hospitals during the time of lockdown. Many of the hospitals has also stopped it's OPD and delaying/cancelling hospital visit of cancer patients to protect them from corona disease. Many questions have been raised and is a big challenge for all the hospitals and doctors such as Would it be right to proceed or begin chemotherapy/radiotherapy/directed treatment/hormonal treatment during these COVID times? What kinds of medical surgery shall be possible during this pandemic in cancer patients? What shall be the ideal time for medical procedure? There is an urgent need to expedite and formulate new methods and techniques to treat, give timely advice and care for the cancer patients. As India & Pakistan are now at peak of corona pandemic, strategies that prove effective against the corona virus need to be devised. There is also a need to gather cancer professionals for implications of treatment strategies for seriously ill patients. Government has to plan the exit strategy for the cancer patients who cannot wait for the treatment.

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REVIEW

Challenges Encountered in Cancer Care and Management During Covid-19 in South Asian Countries

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Abstract

During the COVID-19, the cancer care is one of the most effected fields. The cancer care is either delayed or discontinued during the pandemic because of which cancer patients had to face resource constrain. Limited resources availability during this pandemic led to delay in the cancer diagnosis, undetected/ untreated cases and worse prognosis. The scenario of cancer care is even worse where the south Asian countries including India and Pakistan are considered due to unavailability of experts and adequate resources. Moreover, due to compromised immunity, the cancer patients are advised to restrict the number of visits to their Oncologist. Multipronged strategy to be included in different spheres of cancer treatment and cancer care. The ultimate motto of which is to ensure the well-being of cancer patients. The south Asian countries are framing different recommendations and guidelines to ensure the management of cancer patients through virtual/artificial intelligence modes, so that it shall promote contact less care and management of cancer patients in these countries. Since the beginning of Corona pandemic cancer care and research has been side lined all across the globe and in India & Pakistan as well. This article discusses about effect of SARS-CoV-2 on cancer treatment and nursing in these countries. The strategies for cancer research have also been changed now to cancer care. Urgent need is there to find-out causes of delay in treatment and diagnosis on different stages of cancer. There is a need to minimise the obstacles if the pandemic continues over the coming months.

Keywords: Cancer care- South Asia- India- Pakistan- COVID-19

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Introduction

COVID-19 a pandemic that came as an infectious and contagious disease caused by recently found virus SARS-CoV-2 or Corona virus originated in Wuhan, China on December 2019 [1]. Breaking all the records in Wuhan, soon it spread to the entire world effecting drastically the most developed and medically advanced countries like Italy and United States [2]. The spread of virus from China soon turned into an outbreak causing deaths with respiratory and multiple organ failures worldwide especially seen in immunosuppressed individuals to an extent that WHO had to declare it as an emergency. It declared and advisory stating that old people (above 60 years), kids (below 10 years), diabetic individuals, individuals with breathing troubles and Cancer patients should stay at home in quarantine to prevent themselves from COVID attack [3-4]. From studies conducted on several patients it was reported in Journal of Cancer Discovery in June 2020 that the patients with cancer are more prone to critical illness & die than the infected general population [5]. According to the various cohort studies conducted in a hospital in Wuhan, China from the period of December 2019 till June 2020 it was

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analysed that overall cancer patients admitted during this period, 79% were COVID positive in which 39% died in Intensive care unit while during the same period the general population of admitted to the same hospital was 37% COVID positive out of which 8% died, drawing the hypothesis that cancer patients are more vulnerable to the disease [6].

It was also observed through these cohort studies that the rate of fatality in case of COVID-19 was more due to multiple organ dysfunction than acute respiratory failure despite of the fact that it belongs to the family of SARS virus. This led to the explanation that this virus seriously affected the individuals with weak immunity like in Cancer patients that are undergoing chemotherapy and harmful medications. Such patients on attack with this virus developed multiple organ dysfunction more quickly than cancer patients who were not undergoing any chemotherapy [7].

Among the cancer patients it was found that the patients suffering from lung cancer, hematologic cancer and metastatic cancer stage IV were more prone to fatality due to COVID than nonmetastatic patients [8-9] and had more serious conditions. In addition to that the patients who had in past cancer surgery were also more prone to complexities of COVID to an extent of reversal of cancer or higher death rates [10].

The researchers and medical expert however do not conclude that COVID can cause fatality only to Cancer patients. There are several other factors that also came into light during these cohort studies. It was found that the patients suffering from cancer that died due to COVID were also older in age and some had history of smoking and breathing problems apart from going through chemotherapy [11]. One thing common all the fatal cases was poor or suppressed immune system in entire world including India.

Relation of Immune system with COVID

The ability of Virus to imitate the machinery of its host makes it difficult by our immune system or our defence system to locate any foreign particle especially if we have weak immune system. A healthy individual has strong force of defence cells inside the body that comprises of Major Histocompatibility Complex 1, Cytotoxic T cell, Helper T cells, Natural Killer cells, Macrophages etc. They all act as one big army that acts against any infection in our body. Virus usually release a protein called Viral interferons, that triggers the defence mechanism in the body. Once identified through MHC1 representation on infected cell, the cytotoxic cells release various enzymes to kill the virus by apoptosis. In case if Cytotoxic cells fail then macrophages and natural killer cells directly kill the infected cell with virus as a whole. So, it is seen that the machinery in our body is strong enough to combat any viral attack even if the virus mutates itself multiple times [12-13-14].

In cancer patients the tumour type, the stage of cancer, the age of patient, the type of therapy and supportive medications for cancer decide the rate of probability of contracting the viral infections. Such patients are immunocompromised because of antineoplastic therapy, chemotherapy (Steroid Supportive Medications) and immunosuppressive nature of cancer cells. Such cells alter the innate defence system of the body or may augment an untimely defence response like programme cell death/ apoptosis. Beside this usually the cancer patients that are old have other comorbidities and they have frequent visits to hospitals and nursing care, that further amplifies the complexities making them more prone to COVID attack [15]. So, it is clear from the above discussion that if one has strong immunity then chances of contracting COVID is less or if infected the severity of complication will be less and the recovery will be more.

Management and treatment of Cancer in India during COVID-19

India is a developing nation with upcoming medical facilities and updated medical care and to compare with medical giants like Italy, China, France and US is bizarre. Still India has put forward a strong front in combating the fatality of COVID-19. The ratio of fatality to the population of India effected is lower than the recovery ratio which was appreciated by WHO also [16]. The entire world is fighting the same catastrophe and experiencing the similar failures. For the first time entire world is united to fight the disaster with medical suggestions and practical approach taken by developed nation as the guiding light for health care workers and researchers worldwide [17]. But in India, the shoddy health care infrastructure, lack of good doctors and health care staff, inadequate knowledge and preparedness of pandemic and improper supply of resources has seriously compromised the patient care and safety of health workers. The hospitals being infected with COVID-19 has further worsen the situation. Even the Cancer Institute's scaled back after the reports received from China stated that COVID-19 is worse in Cancer patients [18]. With all these adversities and rationing in patient care the health workers in India designed their innate care delivery strategy especially for Cancer patients. The first strategy that was designed by two healthcare professionals of Tata Memorial hospital for cancer care delivery during COVID-19 as briefly mentioned below [19].

COVID-19 measures at Tata Memorial Centre (19)

1. Management

Formation of a committee known as COVID-19 task force & day by day briefings and formulating action plans.

2. Cancer Care

Avoiding complex medical procedures which requires various blood transfusions and delayed emergency care ward, Use of hypo-fractionated regimes at any point (eg, for breast, prostate, and lung cancers); arrangement of palliative radiotherapy in a uni-division/week by week course of action and Myelosuppressive systematic therapy should be decreased; moving on online specialists whenever possible; When extent of advantage is minimal the action should be postponed.

3. Directed- Patients

Checking camps to be made outside the cancer centre which will lessen patient visits, limitation in family members & companions in outpatient department and inpatient department, while routine follow ups should be changed to an online mode i.e. tele counsel.

4. Alerting Hospital

Foundation of set working systems for suspected cases/affirmed COVID-19 disease, body temperature facility and making of isolation area

5. Staff-Directed

Paid leave to be given to the individuals with high-risk (old aged staff, staff who is consuming immunosuppressive drugs, and pregnant staff); Shift changing of employees to guarantee an alternative in case of an occurrence of isolation and Provision to shift staff in emergency bus who are not able to arrive at work as a result of the transportation lockdown.

In India the hospitalisation is being given to most priority cases and mostly people if else healthy with no complications are advised self-isolation and quarantine for 14 days with basic medical and civic facilities from the state government. However, with cuts in hospitalisation and basic medical facilities the cancer patents are more prone to risk that otherwise is not life threatening at once. The cancer institutes and hospitals all over India are giving treatment first to the more curable cancer cases effected with COVID-19 that would benefit from the treatment over the non-curable ones that were as such in palliative care and the treatment would give only marginal effect. The decision helped in saving further the life of cancer patients with treatment for COVID-19 along with lifesaving cancer treatment. The decision seems harsh but in this pandemic time this is the only way to avoid regular cancer screenings and follow ups of cancer patients as to safeguard them from nosocomial infections related to infected hospitals and infected healthcare staff [20].

The establishment of National Cancer Grid that is the online web network of all the cancer centres in India was made by Tata Memorial Centre. This helped in sharing information and health protocols with the cancer specialist all over India through weekly webinars and webex. This is one of the most remarkable steps under Cancer Care strategy during COVID-19 by an institute. It has brought all the Cancer treatment and Preparedness for COVID-19 under one roof so that everywhere in India the cancer patients at this time are given similar lifesaving treatment [21].

The measures that are being taken by the health department of the State for safeguarding cancer patients is appreciable however, more important is preparedness of cancer patients by providing them complete knowledge of COVID-19 and its precautions. Informing them about basic hygiene, self-isolation, taking natural immunity boosters along with prescribed medicines and guiding them the new hospital care and visit only when it is very urgent [22]. To avoid increase of Coronavirus in Cancer patients the WHO guidelines i.e. isolate, test, treat and trace have to be adopted stringently for this Aarogya Setu app by Government is also very helpful. Through this app a Cancer patient can be aware of any active cases near his locality and the contaminant zones around his locality [23-24].

The Cancer centres through online follow ups with their patients are planning the treatment for them revolving around the strategies by Tata Memorial Centre [19], that has been broadly divided in categories: a) planned surgery- if required as per priority or can be delayed, b) undergoing immunotherapy, radiotherapy or chemotherapy- if necessary or can be delayed with specific life-saving cancer medications for time being, c) Stem cell transplantation- If not life threatening can be delayed and those with recent transplant should be kept in isolation to prevent them from COVID-19 infections, d) Antiviral therapy- this usually generated prophylactic response so yet it has to be confirmed that such therapy can be given to immunocompromised individuals, hence it should be avoided, e) antiviral medicines like Hydroxychloroquine, remdesivir7 etc are being given for treatment of COVID-19 but these drugs are not designed for COVID treatment so to try them on cancer patients is very risky and lastly (f) plasma therapy- The therapy involves transfusion of plasma cells carrying antibodies for COVID-19 from cured COVID-19 warrior to infected COVID-19 patient, thereby generating quick immune response in that patient and safeguarding him against this deadly virus [25]. Recently Delhi CM Arvind Kejriwal got approval for Plasma Therapy from ICMR to be conducted in hospitals named Rajeev Gandhi Super Speciality and LokNayak Jai Prakash for cancer patients after a successful clinical trial. It helped to moderate infected COVID-19 patients and is able to save their lives but in severe cases even this therapy is failing. So, Rajiv Gandhi Cancer Research Hospital is using this therapy on those cancer patients that are not very fatal and have chances to survive. These patients after therapy are given pulse oximeter to monitor their oxygen level daily [26].

So, it can be clearly stated that the effect of Cancer treatment during COVID-19 is shifted to Elective and Selective mode. The cancer centres as per WHO guidelines will isolate the patient first and if tested positive for COVID will be selected for life saving treatment and the surgery for the treatment of the cancer will be postponed by surgeon under elective surgery discipline that is depicted below [27]:

1. Examination of surgical need of cancer patient
2. Preparedness of Hospital with logistics and resource for the surgery
3. The consequences post-surgery to be mapped and aware to the patient
4. If delayed or postponed what risk it may impose to the patient
5. After analysis of above four points the final decision has to be taken.

This elective surgery discipline is very helpful in current scenario of cancer treatment in India as they are selected for cancer surgery only if they have two COVID-19 tests as negative after 72 hours. This step was taken because the cases of asymptomatic carriers is increasing in India in that case if inert COVID-19

patient undergoes surgery it may lead to severe critical complications and immune suppressions in individuals leading to their death. So, it is advisable till it is not necessary all the surgeries should be deferred [28].

The nature fury or a bio weapon, the source of COVID-19 is still untraceable but the magnitude of its occurrence and prevalence has made it listed in one of the most-deadly disease in the world. It's completely delusional as to when the COVID-19 outbreak will be over so every state is doing it preparedness post COVID times as well. Healthcare professionals are being given psychological help and all the possible support and resource so that they remain to be the COVID -heroes. The researchers, DRDO, CSIR, ICMR and all the research labs in India are trying hard to develop a drug or vaccine to eliminate this virus. The Government on other hand has increased testing laboratories, makeshift isolation centres and hospitals while stocking the antiviral and antimalarial drug in store [29]. The population of India are utilising their lockdown period in developing immunity and hygiene in themselves and guiding others around them to do the same. Probably on brighter version of life Post COVID-19 the cases in Cancer should reduce as people are trying to be more fit by doing yoga and exercises. They are more hygienic and eating healthy food and maintaining balanced diet that builds their immunity. So, hope for a brighter future for India post COVID-19 [30].

COVID-19 in Pakistan

Corona virus started spreading in Pakistan in Late February, 2020. Initially the number of cases remained low as China borders closed and check on the International flights were performed. Later at the end of February it started rising as 3000 religious pilgrimage returned from Iran and Saudi Arabia, with many are the carriers. Although the Government officials were strongly criticised for chaotic response but even then, most of the people were quarantined in sub-optimal conditions. Some countries including China also helped the Pakistan Government for coping the condition. At the end of March an increase was seen as most of the Pakistanis overseas from heavily infected countries travel back [31-32]. Initially the complete lockdown started since 13th of March. The social distancing measures were advised, large gathering of religious congregation was not prescribed. The month of March and April remained closed for all educational institutes, offices and business. Nowadays, country is in a state of partial lockdown and they are reluctant for a complete lockdown because of fear of economic havoc as 25% of the population are on daily wages. New facts and data of India also suggest this type of fear is most likely to be found in the developing Asian countries [32]. Stabilizing the economic loss in front of the COVID-19 is an inevitable task and Government like Pakistan which falls under low and middle income is already facing it.

Cancer care scenario in COVID era

Pakistan, is very populous with a head count of 220 million people. With each passing year the rise in the new cases of cancer also increased each year with 200,000 each year. There are very few centres in this country. The main hospital that is dealing with cancer sufferers are Shaukatt Khannum Memorial Cancer Hospital and their centres for research. These hospitals are also overburdened with the patients. Every year 45,000 new patients come to register for treatment in these research hospitals. Due to the limitation in the capacity only 10,000 new cases are able to be accepted while the remaining cases are declined. Pakistan also has more than 11% of the patient's which falls under category of child and sufferers are not only of Pakistan origin but also from neighbouring countries as Afghanistan [31-32-33-34].

Although the cancer hospitals accept the patients free of charge irrespective of the race and nationality. But there is a lack of availability and resources to deal with such larger population of people. The national budget and health structure if fragile and patchy. With the advent of corona pandemic, the situation seems to become more worse as the country already has limited ventilators of 4000 working ventilators for a population of about 220 million.

Balancing the risk of COVID 19 with economic crisis, and starvation, and this task is unavailing for low- and middle-income countries people. Cancer care is a complex, expensive, time consuming and it is becoming difficult now for the patients and their families. The care of cancer is a complex procedure, it involves expensive and time consuming and is difficult even at the best of times. Economic uncertainty, as well as obligations on the normal and ongoing clinical check-ups because the pandemic complexes the complication of cancer [31-32-33-34].

Cancer care is a prolonged, and expensive treatment. It is difficult for the patients and their families to cope with it in normal circumstances. At present due to economic uncertainties and restrictions on the travel worldwide and within the country the care and treatment of this disease become more difficult. At the second largest city Lahore we have just 200 beds in Shaukat Khanum Memorial Cancer hospital, although it is considered a large hospital by public sector standards. Although for COVID care there are 1,000 + bed hospitals in the city that have greater capacity to offer such care quarantine services. One of the major issues lacking in this country is ICU beds and ventilators. Shaukat Khanum Memorial Hospital devised a plan for increasing the number of ventilators from 11 to 15 by using available resources so that it reaches up to 50 ventilator beds. While normal inpatient beds have already converted to an ICU, to allow this expansion of beds [35-36].

The provincial Government is also supporting the cancer hospitals by giving the major equipment as primarily ventilators and cardiac monitors to monitor the cancer patients to operationalize the beds. Most of the hospitals are not taking the cancer patients most were not able to travel, in any case—and rapidly curtailed the visit of these patients for normal check-ups. The emergency cases including chemotherapy, radiation therapy is still continued. In addition to this a third inpatient unit has been opened for the patients having the coronavirus who are

not in that stage to need an ICU, or have just recovered from ICU. The Shaukat Khanum hospital has recently made a decision that any spare beds are going to be used by the patients of corona patients who are unable to pay for their treatment [35-36].

Molecular pathology labs have started providing services for COVID-19 patients testing as part of effort against the coronavirus. Radiology services and essential imaging services are continued for COVID patients. While all elective services and screening procedures like endoscopy has been stopped. There is a nationwide shortage of the protective equipment's for COVID they include surgical gloves, N95 masks/ filtering face piece particle mask. Some of the developed textile industries has taken a step and started manufacturing gowns and other protective clothing, and several local manufacturers are now able to produce manufactured gowns and personal protective clothing (PPE). Efforts of producing N95 masks are also commenced but there is a concern to whether this can be equally efficient in current pandemic situation [31-32-33-34-35-36].

Pakistan National Disaster Management Authority has given the task to buy the personal protective clothing and then distribute to the needy people. The demand of PPE although has been increased globally and there is a global shortage and enormous demand everywhere in the world. In Pakistan there is a culture of attendants to accompany along with the patients. Normally three to four patients accompany to each patient. Now there is a restriction on the coming of attendants with the patients. There is also the initial screening available for all the people entering the hospitals by checking the common COVID-19 symptoms including fever, cough and breathlessness. All those patients are referred in separate building outside the main hospital. Following further treatment such patients are advised to self-isolate until their results are available. Moreover, the triage centre for patients are also opened 24 hours and number of patients seeing per day is increasing. The separate facility in hospitals like Shaukat Khanum and other cancer hospitals has helped the patients to be divided on the basis of treatment and now are identified easily. Separate routes of entering for chemotherapy patients are now available as to protect the chemotherapy patients or the patients having the severe cancer progression can be protected. This is now helping and protecting the cancer patients as till date the rise of the corona patients is increased in Pakistan with 1000 patients per day. There is a need in various hospitals to designate the parts as patients with COVID infection (red) suspicious (yellow) and non COVID (green) thus the easy identification and care could be established [35-36]. Most of the cancer and other hospitals has established the virtual clinics for identifying and separating patients and normal individuals. Pakistan is a country with very good mobile networks so almost 90% of the people have the mobile coverage. Pakistan has the highest rate of mobile penetration in South Asia so consultations are also being carried out by using the WhatsApp calling systems. Although many patients have not the WhatsApp calling but their response is positive with the relief that they are in touch with the medical specialists. Prescriptions and advices are also sent by using the SMS and screenshots services. The main patients facing the problem is about the purchase of medications of cancer as well. The people are in the financial crisis and supply of drug also changed. The strategies for treating the cancer patients having corona virus has also been changed. There is a need for revising the protocols for treating any patient of cancer affected by corona. Most of the liver cancer patients has been asked to take medications like oral sorafenib for the ones who do not need the immediate visits [31-32-33-34-35-36].

Those patients who are on chemotherapy have to wait for a longer period of time than the normal routine or they may be treated with the additional cycles to cope with long waiting time. In Pakistan since the beginning of COVID-19 in March 2020 new patients admitted for cancer treatment has been reduced to one third. The patients already having the radiation treatment has been reduced to half. According to one report out of normal treatment where 800 elective surgical procedures has been carried out since lockdown condition the rate of that procedures goes down to 20 [35-36].

There is also a need for counselling sessions for the healthcare and support staff who are working in this situation. Although some support session for cancer patients has already been setup by using the telemedicine facility. Most of the cancer clinics and hospitals has seen the rapid drop of the clinical income which are derived from the diagnostics services and pathological collection. Some of the hospitals have also cut down the salary of the staff by 10%. Ranging from 25% reduction of highest paid and 5% reduction of lowest paid workers. New doctors and cancer professionals are also now hard to train and retained in resource limited environment. The patients with some associated reasons are only admitted based on variety of factors as age, availability of appropriate drugs, likelihood of having the complete cure etc. While most hospitals have already developed the system to accept the patients based on the severity of disease. To date Pakistan has 199K confirmed cases with 4000 deaths and 2729 critical patients. The cancer treatment and check-ups are now reduced which will affect the survival and prognosis of cancer patients. There is a need to keep going the normal check-up and facility availability to cancer patients so that they may not suffer from corona pandemic. Immediate strategies for care for cancer and corona effected patients need to be devised [31-32-33-34-35-36].

Challenges in the minds of people: Questions raised in people's mind due to fear

Patients have developed fear, a very dark fear due to COVID-19. If left unanswered these may cause anxiety in public and turn the situation in the worst. Therefore, it is important to address these questions.

"Is cancer or COVID-19 going to execute them?"

"What might be the smart solution for patients to do?

"Consulting doctors are saying they have to hold and sit tight for the treatment?"

"How might they save themselves?"

There is a big question in the minds of patients "What

if cancer increases, will all the past treatment they had will be effective?" "No one is able to tell anything even doctors are scared to treat cancer patients. This obviously portray stress and a decrease in patients to the hospitals.

In conclusion, care for cancer patients has been majorly hit all over the world. In India and Pakistan as well, cancer care is affected badly. The serious issues in these times of COVID is faced by Cancer patients because of their weak immune system as they are more prone to this Corona Virus disease which the world is facing. Mortality of cancer patients has increased as cancer treatment has been stopped and many hospitals has been totally converted to COVID Hospitals for treatment of Corona. Travel limitations was also imposed by the central and the state government of India which also reduced access to the hospitals during the time of lockdown. Many of the hospitals has also stopped it's OPD and delaying/cancelling hospital visit of cancer patients to protect them from corona disease. Many questions have been raised and is a big challenge for all the hospitals and doctors such as Would it be right to proceed or begin chemotherapy/radiotherapy/directed treatment/hormonal treatment during these COVID times? What kinds of medical surgery shall be possible during this pandemic in cancer patients? What shall be the ideal time for medical procedure? There is an urgent need to expedite and formulate new methods and techniques to treat, give timely advice and care for the cancer patients. As India & Pakistan are now at peak of corona pandemic, strategies that prove effective against the corona virus need to be devised. There is also a need to gather cancer professionals for implications of treatment strategies for seriously ill patients. Government has to plan the exit strategy for the cancer patients who cannot wait for the treatment.

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SHORT COMMUNICATION

Cancer Care Challenges in COVID-19 Pandemic: A Prospective from Tertiary Cancer Centre in Eastern India

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Introduction

The whole world is witnessing the Corona virus disease-2019 (COVID-19) pandemic. India is having presently 5,08,953 cases of COVID -19 and 15,685 patients deaths as on 25th June 2020 and the total number of cases in Jharkhand, a state in the eastern zone of the country is 2,207 with 11 deaths [1].

Since the detection of 1st case on 29th January 2020 in India, there was nationwide fear, as we were observing the fatalities per day in other countries like China, Italy, the US, etc [2]. Subsequently, In India complete lockdown was announced from 25th March 2020. There was high fear among hospital personnel being at the risk of catching an infection while taking care of the patients, and there have been reports of infection and deaths of many health care workers while delivering their duties [3]. In Jharkhand, our tertiary care facility also followed the health advisory and suspended outdoor facilities, cancelled routine surgeries, and started teleconsultation to decrease the overcrowding of patients and attendants in the hospital to decrease the risk to one and all, however, emergency services were available for all. With this step, patients' footfall to hospital decreased but simultaneously in the oncology setting it was quite challenging as this would upstage the disease in many patients. So, prioritizing strategies were made to combat this challenge to have the best possible management of cancer patients. Also, there are reports of high fatality in patients having cancer and other co-morbid conditions like diabetes mellitus, hypertension, chronic kidney disease [4].

Our hospital has a dedicated separate block for COVID patients' diagnosis and management. All patients coming for oncology consultation were sent for COVID-19 screening in the hospital. A thermal screening of all patients was done before allowing their entry to Oncology building.

Real-time polymerase chain reaction (RT-PCR) testing for COVID-19 was done in cancer patients as per the national Indian council of medical research (ICMR) guidelines based on their symptoms, history of travel, and/or history of contact with COVID-19 positive patients [5]. The routine practice of social distancing, wearing a mask, face shield, and practicing hand hygiene by all hospital staff and patients were strictly followed. Regular sanitization of the workplace was carried out regularly. Hospital staff wore personal protective equipment (PPE) judicially as per the institutional standard protocol. Till now none of our cancer patients were found to be COVID-19 positive.

After screening patients were evaluated in the oncology department for the needful. New patients underwent diagnostic workup and old patients were planned for awaited treatment. As the oncosurgery department was still not operable for routine planned surgeries at our hospital as per the health advisory, patients were referred for neoadjuvant chemotherapy (NACT)/ chemo-radiotherapy(CT+RT) as per the case details to slow down the disease progression and to buy some time for surgery. Also, many of our head and neck cancer and other patients come with an advanced presentation, so, in that case, NACT/CT+RT would be the most suitable treatment. For chemotherapy, there was a mandatory prescription of Filgrastim/ peg-Filgrastim post-chemotherapy schedules to decrease the risk of neutropenia and subsequent complications in this COVID -19 time. Also, general advice for the intake of a well-cooked nutritious diet, lukewarm saline gargles, and maintaining good personal care was given. Patients who were on an oral form of treatment as hormone or immune-chemotherapy, they were prescribed for 2-3 months duration at once and asked for blood monitoring at local labs. This further reduces the patient volume in the oncology setting.

Cancer patients requiring radiotherapy were assessed for the aim of treatment. Any cancer patient with low-risk

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features, for them radiotherapy can also be delayed for 3-4 weeks [6]. In general radiotherapy in adjuvant and radical setting goes on for 5-7 weeks depending on the site of cancer. In the current pandemic time, all radiation oncologists are working out to decrease this duration to a shorter period by carefully assessing the target coverage and organ at risk toxicity. So, we are changing to hypo-fractionation schedules from the 1.8-2Gy/# conventional protocols where feasible to decrease the patient stay in and around the hospital and thus reducing the risk of COVID-19 infection to all involved personnel in the care of patients. We all know the non-inferiority results of hypo-fractionation schedules in breast and prostate cancer in curative settings and these are widely practiced as a standard of care. There are recent recommendations made by ASTRO-ESTRO for head and neck cancer radiotherapy of hypo-fractionation schedules to ease this pandemic situation [6]. We are also practicing 55Gy/20#- 60Gy/24#, 5# per week in head and neck cancer radiotherapy, and this prescription dose are decided as per the TNM staging and risk factors present. Patients requiring palliative radiotherapy for brain metastasis, bone metastasis, and spinal cord compression are usually treated over 1-3 weeks. However, at our center during the current scenario, we are practicing mostly single fraction or 5 # radiotherapy for such cases.

Throughout India COVID-19 is in peak phase now, with the present-day scenario which is horrifying with 18000-20000 cases per day with 350-400 deaths, however, in Jharkhand, the per day cases are in the range of 30-90 [1]. But among all these odd figures, we have a good recovery rate of 71% in Jharkhand while 58% of this virus in India [1]. We, Oncologists, know this is a tough time for all and additionally, this virus is going to stay for long in the world, till the successful launching of a vaccine against this virus. Till then we have to face this challenge with all wiseness and appropriate strategies in cancer patient care.

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SHORT COMMUNICATION

Make Self-help Psychoeducational Programs for Breast Cancer Patients COVID-19 Proof

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Abstract

The Covid-19 pandemic has significant consequences for the many self-help psychoeducational programs for patients with cancer (symptoms), especially in Low-Middle-Income Countries. We recommend several measures to adapt these programs to the COVID-19 era, such as the use of mobile versions, the addition of preventive measures to be taken by health care providers and patients concerning a hospital visit and the inclusion of psychological advice for coping with COVID-19 related stress. In this way, the double task of preventing the (progression of the) target disease and a contamination by COVID-19 might be optimally fulfilled.

Keywords: Cancer- Oncology- Breast- Covid-19- Indonesia- Psychology- Self-help

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Introduction

The Covid-19 pandemic has significant consequences for the health care all over the world, and among those are the many self-help psychoeducational programs that support cancer patients to cope with their psychosocial problems and to increase adherence to medical procedures.

Psychoeducation refers to therapeutic approaches that involve information giving and receiving, discussion of concerns, problem-solving, coping skills training, expression of emotion, and social support [1]. Psychoeducation has emerged in practice as adjunctive treatments for cancer in which patients and families are struggling with different challenges associated with breast cancer (BC) diagnosis and treatment [2]. Psychoeducation is considered to be less expensive, more easily administered and potentially more accessible than conventional psychological interventions [3].

Most psychoeducational programs for cancer patients focus on coping with the anxiety, depression and stress due to the disease. Information about the disease and the associated health care are often provided as well. Some programs aim at improving the patient's adherence to the medical guidelines. The format of these programs can be face-to-face [4], web-based [5], using a manual [6] or a combination [7].

Our group developed a culture-sensitive self-help psychoeducational program, named PERANTARA, for women with BC symptoms in Indonesia [8]. 'PERANTARA' is an Indonesian acronym which stands for: 'PEngantar peRAwataN kesehaTAn payudaRA, meaning: 'Mediator for the Treatment of Breast Health'. It aims to motivate of women with BC symptoms to comply with diagnostic procedures and to seek social support. It consists of printed material with information about symptoms and actions to be taken and of audio-visual material with testimonials of two BC survivors. Our recent publication [9], based on data from the pre-COVID-19 period, showed that our program had a significant effect in shortening the time these women took to visit the hospital for diagnosis and treatment. The moment, however, we were planning to implement our program in the local

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hospitals in Indonesia, the COVID-19 pandemic turned these into potential centres of COVID-19 contamination, because the medical health care, understandably, was not prepared by adequate methods of protection. This situation put many patients with cancer symptoms in a Scylla and Charybdis condition, where a trade-off had to be made between postponing a hospital visit with the risk of a cancer progression, and a hospital visit with the risk of infection by COVID-19. Several patients who are aware of this risk prefer to stay at home because of the fear for contamination. It also made the core message of our PERANTARA program ('visit the hospital as soon as you perceive symptoms that may indicate BC') too simple and risky. This situation is, in particular, a problem in Low-Middle -Income Countries (LIMCs), where medical care lacks enough personnel, tools and resources. In Indonesia, for instance, the medical care for cancer patients has been delayed in order to be able to meet the demand for care for COVID-19 patients.

We, therefore, advocate that self-help psychoeducational programs like ours, aiming at reducing patient delays and providing patient support, should be adapted to the new situation. The role of such programs can then even become more important as a tool for helping patients in a situation of lock-down than before.

The publications of the editorial boards of the Indonesian Journal of Cancer [10] and Breast [11] can be considered as a point of departure for the adaptations of self-help programs. These publications provide guidelines, including selection criteria and prioritization of hospital visits, for cancer diagnosis and treatments, according to the pandemic scenario in different countries and /or regions.

When we translate their recommendations into specific adjustments of self-help psychoeducational programs, like our PERANTARA for patients with BC symptoms, we propose in line with their advice the following:

1. Self-help psychoeducational programs should also be provided by mobile phone.

2. Mobile versions of self-help psychoeducational programs should be created that follow the COVID-19 prevention protocols. After recognizing BC symptoms when using such programs, the patient should be able to arrange an online-consultation with a specialized health care professional first (the sooner the better) to estimate the nature and severity of the symptoms, to decide whether a hospital visit is warranted.

3. When this anamnesis indicates that the severity of the symptoms justifies a physical examination and/or treatment at the hospital despite the COVID-19 situation, information must be also provided on the preventive measures taken by the hospital and on those to be taken by the patient against COVID-19

4. The advice to go to hospital for diagnosis or treatment should be tailored to the patient's medical condition and the current health care situation (in particular regarding COVID-19), which may vary by country and region.

5. The programs should include instructions regarding on-line consultation with a specialized health care professional.

6. Instructions to prevent COVID-19 contamination, not only during the hospital visits but also during the journey to and from the hospital, which can also be quite long and risky in LMICs, should be included.

7. It is important to add psychological advice to the self-help programs, which not only focuses on cancer, but also on COVID-19 related fears. Possibilities for referral to more extensive psychological help by telepsychology should be provided as well.

These adaptations imply a number of changes in the medical health care system too. Facilities for on-line contact with medical and psychological interactions need to be developed and sustained. It is crucial, as is also emphasized by Curigliano et al (2020), that such adaptations should be made in a multidisciplinary collaboration of physicians (in particular oncologists), nurses, and psychologists from the country and region involved.

The 'new normal' situation changes rapidly and in a different pace between regions and countries. For example, several hospitals in Indonesia have now separate 'green zones' for patients without COVID-19 symptoms and patients will be checked before entering by temperature screening and questionnaire. It is, therefore, important to monitor the changes in the hospital management of patients with BC symptoms, which are due to the COVID-19 pandemic. The outcome of the monitoring can have implications for the patient's behavior, such as finding the safe way to visit the hospital (how, where and when), and for their coping with COVID-19 related stress. Such implications should lead to corresponding adaptations in the psychoeducational programs. Since these changes may differ between regions in a large country, such monitoring should be done at a regional level as well

The recommendations presented above will be implemented as soon as possible in our PERANTARA program for patients with BC symptoms in Indonesia. We expect these also to be useful for self-help psychoeducational programs in other patient groups, and in other countries. In this way, the double task of preventing the (progression of the) target disease and a contamination by COVID-19 might be optimally fulfilled.

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CASE SERIES

Transmutation of Spiritual Credence During COVID-19 Era in Cancer Patients: A Case Series

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Abstract

Background: COVID-19 pandemic has afflicted cancer patients on various fronts including spiritual domain. The case series tries to highlight the spiritual beliefs and challenges faced by cancer patients and the transformation which has occurred during pandemic. **Methods:** Thirty consecutive cancer patients who attended outpatient clinic of cancer pain and palliative department were assessed on spiritual front through nine questions and on the basis of which their perception about spirituality, health problems, role of pandemic in transformation of spiritual beliefs and their coping mechanisms were analyzed. **Results:** Most respondents related spirituality to almighty. Half of the cases blamed karma, fate and God for their suffering. Signs of transformation in spiritual credence during pandemic was evident in the form that majority could not attend their places of worship, were having lack of spiritual clarity and developed feeling of fatalism. For coping with the stress and anxiety majority resorted to path of prayer and chanting at home, with few having belief in helping out others and participating in spiritual community sessions to overcome their problems in life. **Conclusion:** Spiritual domain of the patients is often an overlooked component by the clinicians during their examination. But maintaining a good spiritual health is as important as physical health for an overall better outcome in cancer patients and should be catered for providing a holistic care.

Keywords: Spirituality- cancer- COVID-19

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Introduction

The Corona Virus disease 2019 also known as "COVID-19" was declared a pandemic by WHO on 12th March 2020 [1]. It has created havoc all over the globe and impacted every country on various fronts including economic, social and political [2]. In India also the count is rising steadily. The patients with underlying serious health conditions for example cancer, have an increased risk of admissions into intensive care units [3-4]. The estimated case fatality rate in cancer patients with COVID-19 is 6%, [5] as compared to 1% among the general population [6]. With the estimated number of cancer cases in India being approximately 2.25 million the impact of this pandemic on cancer patients will be grave affecting both survival as well as quality of life [7]. The diagnosis of cancer in itself creates a feeling of desolation in patient's life. It not only affects the physical and mental well-being of the patient and the caregivers but also affects the spiritual domain. Patient through the whole journey of cancer diagnosis and treatment undergoes myriad of emotions with numerous questions arising in mind on meaning and purpose of life. Spirituality has been defined as, 'An inherent quality of all human beings that drives the search for meaning and purpose in life, involves relationships with oneself, others, and a transcendent dimension [8]. It has been identified as an important pillar of health and well-being of the cancer patients and leads to improved quality of life with the help of spiritual practices like meditation [9]. There is paucity of literature exploring the spiritual beliefs and challenges faced by cancer patients during the novel COVID-19 pandemic. Through this case series we would like to highlight the transformation that has happened in the spiritual beliefs of cancer patients

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during this pandemic. On the basis of our assessment we also suggest few solutions which can be incorporated by the clinicians in their practice to help the patients overcome the spiritual dogma.

Materials and Methods

Thirty consecutive cancer patients who attended the outpatient department of cancer pain and palliative clinic of a tertiary care centre were included in our case series. Basic demographic information in form of age, gender and address was noted along with diagnosis and ECOG (Eastern Cooperative Oncology Group) performance status. The spiritual assessment was done with the help of nine questions which assessed the spiritual and religious beliefs, the level of distress they were undergoing and their coping mechanism (Table 1).

Results

Out of thirty respondents, fourteen were females and sixteen were males. Table 2 highlights the site of malignancies of the patients. Eight cases (26.66%) belonged to ECOG (Eastern Cooperative Oncology Group) physical status III, rest twenty two cases (73.33%) belonged to ECG II.

Sixty percent (18) of the patients when asked about their perception of spirituality answered that they feel it is a sense of connection to some higher power or almighty. Seventeen percent (5) of patients felt that spirituality is connecting with oneself and others. For equal number (5) of respondents' spirituality gives them purpose of life (Figure 1).

Regarding the perception of patients about their health problems fifty percent (15 cases) did not blame anyone for their disease or the current ongoing COVID pandemic and said that they are sad about what is happening with them and what is happening around in the world. One third (10 cases) of the respondents blamed it on destiny and karma together. Only two cases blamed God for all the sufferings (Figure 2).

The COVID-19 pandemic has brought tremendous change in the spiritual practices of the cancer patients. Eighty three percent of cases (25) felt that they are not able to go out to their religious places to devote time to God. Fifty percent of cases (15) felt that there is lack of spiritual clarity. Seven cases had feeling of fatalism. Eight patients reported both lack of spiritual clarity and sense of fatalism Figure 3.

To deal with all the stress related to disease and ongoing COVID-19 pandemic patients also expressed their coping mechanisms. Fifty percent (15 cases) felt that their belief in God gives them strength. Sixty six percent patients (20 cases) use praying or chanting to deal with the stress and anxiety. Eight patients were grateful for life in general and had no qualms about the whole disease. Seven patients felt that the there is immense role of their spiritual community programs and sessions in providing them strength which they are attending online nowadays. One sixth (5 in number) of cases felt that helping out other people in the times of need gives them solace (Figure 4). Sixty percent (18) of the respondents told that that the health care teams should address the spiritual concerns during the hospital visit.

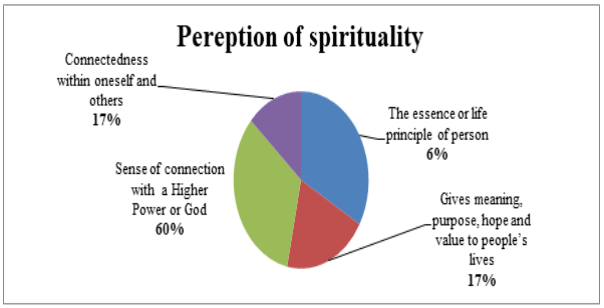

Figure 1. Perception of Spirituality

Table 2. Details of Site of Malignancies

Site of Malignancy	Number of cases (Percent)
Head and Neck Cancers	8 (27%)
Genitourinary cancers	4 (13%)
Hepatobiliary cancers	3 (10%)
Hematological malignancies	3 (10%)
Breast cancers	7 (23%)
Bone tumors	3 (10%)
Thoracic malignancies	2 (7%)

Table 1. Spiritual Assessment Questions

1. What is your perception regarding spirituality?
2. What do you think is the cause of the health problems?
3. How do you cope with the stress and what is your source of peace?
4. How the spiritual belief helps in taking care of oneself?
5. What is the role of the spiritual community in your life?
6. What are your current spiritual practices?
7. What gives you sense of fulfillment in life?
8. How has the pandemic affected the spiritual beliefs and practices?
9. Do you think that the health care team should address the spiritual concerns during the hospital visit?

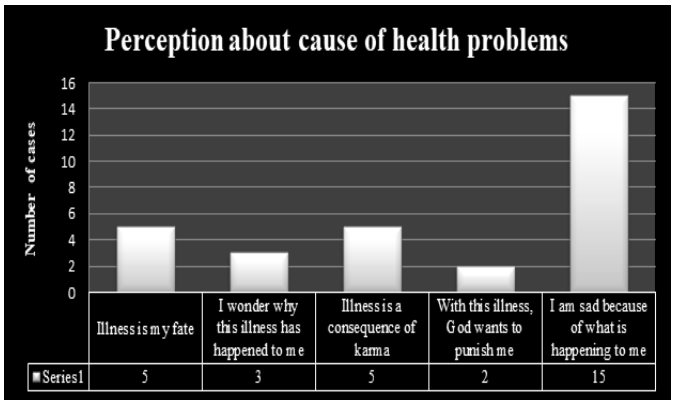

Figure 2. Perception about Cause of Health Problems

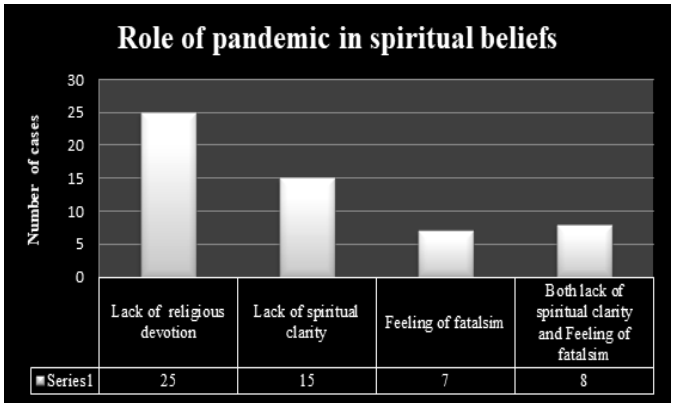

Figure 3. Role of Pandemic in Spiritual Beliefs

Discussion

Cancer patients and their caregivers face lot of hardships and challenges throughout the process of diagnosis and treatment. It takes a toll not only on the physical health but also on the emotional well-being. Ongoing novel coronavirus pandemic has made the task even more uphill for all the cancer patients. To deal with the emotional stress spirituality is often contemplated as a helping hand and makes decision making easier [10]. The case series tries to highlight four things- the perception of spirituality, the view point of the patients about their disease and ongoing pandemic, the transitional shift that pandemic has caused in their spiritual practices and their coping mechanisms. In our case series, majority patients felt that for them spirituality means connection with almighty. Even though religion and spirituality are two distinct entities but they are often conflated into one. Cohen et al [11] also suggested that religion is one of the components of spirituality and same is evident from our series. Half of the patients did not put blame on anyone about their disease, but at the same time the other half said that the current pandemic and all their sufferings is because of fate, their past karmas and because of almighty.

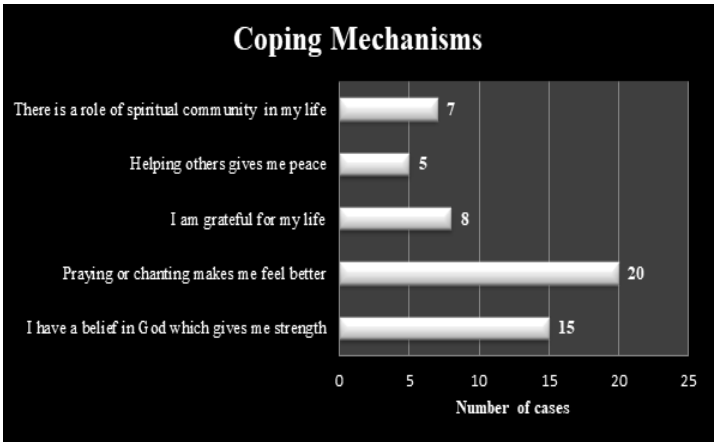

Figure 4. Coping Mechanisms

This highlights the fact that almost all the patients are either worried about their situation or are trying to find answers to their problems through God. Almost sixty percent cases emphasized that they want the health care workers to discuss about their spiritual concerns and needs during their hospital visit which is often an overlooked component in our day to day clinical practice. It thus illustrates that spiritual issues needs to be addressed in the broader context in all the cancer patients [12]. It gives them a sense of belief and impetus to lead their life in a more positive way. As far as the COVID-19 pandemic is concerned, whole world has been inflicted, more so the patients who are suffering from debilitating illness like cancer. Cancer patients who are already striving hard to cope with their primary illness also have to worry now about getting affected by corona virus infection because of their immunocompromised state. Because of policies of nationwide lockdown majority respondents felt that they could not visit their religious places of worship, developed lack of spiritual clarity during these tumultuous times and had feeling of fatalism. People have been forced to remain indoors most of the time but now have started to pray from home and use liturgy and prayer resources provided to them. People have started to understand that compassion, kindness, sympathy and caring are the spiritual virtues that will help them to sail through. To deal with the stress and anxiety of disease and the pandemic, patients are using various coping mechanisms in the form of prayer and helping out others. Few were grateful to life in general whatever may be the circumstance in their life, rest felt that God and their spiritual community and sessions provided them strength and hope. After assessment of the spiritual needs, beliefs and challenges we suggest that all cancer patients should adopt spiritual care plans in the form of practices like meditation. They should try to follow their hobbies like art, craft, music, writing whenever feasible and should try to participate in spiritual community programs. From healthcare setup point of view clinicians should engage in the discussion about the spiritual concerns during the patient's visit to the hospital and may refer the patient to spiritual professional if he/she wishes to. Clinicians may also adopt hope stimulating strategies in the form of developing interpersonal connect with the patient. Patients should be encouraged to attain small specific goals. This will ultimately help them in optimizing their courage, determination and serenity.

In conclusion, the case series highlight that addressing the spiritual needs is an important component of the whole treatment strategy in cancer patients. Cancer patients face lot of challenges on spiritual front also apart from the physical domain. COVID-19 pandemic has aggravated the challenges and problems the cancer patients are already facing. Cancer patients perceive spirituality in different ways, have different beliefs related to their disease and have different coping mechanisms but the novel corona virus pandemic has led to transformation and transmutation in their spiritual practices and beliefs. It thus becomes imperative for the health care professionals to understand the changing needs of the cancer patients and the care givers during the pandemic so that holistic health care services can be provided to them.

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PERSPECTIVE

Zinc Supplementation Prevents the Complications of COVID-19 Infection in Cancer Patients

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Abstract

Novel coronavirus" SARS-CoV-2 is rapidly spreading worldwide with a significant mortality rate. In the crisis of COVID-19, cancer patients are seen as a very weak group and this is because of their weakened immune system and hence we aim in this research to show the importance of zinc as a buffer against cancer in COVID-19 for cancer patients. Zinc is an essential trace element that is crucial for growth, development, and the maintenance of immune function. zinc supplementation decreased and generation of inflammatory cytokines. zinc supplementation should have beneficial effects on cancer by decreasing oxidative stress, angiogenesis and induction of inflammatory cytokines while increasing apoptosis in cancer cells. zinc supplementation implemented to improve the antiviral response and systemic immunity in patients with cancer diseases. With the multiple doses approved from zinc, we suggest that there be an supplement in zinc by 50 mg / day for three month with each treatment for cancer patients, in order to strengthen the immune system to prevent the serious effects of COVID19 infection.

Keywords: COVID-19- Cancer diseases- Zinc supplementation- Immune system

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Introduction

Novel coronavirus" SARS-CoV-2 is rapidly spreading worldwide with a significant mortality rateSARS-CoV-2 is a new coronavirus called acute respiratory syndrome, and has been identified to be the cause of pneumonia [1]. In the COVID-19 crisis, cancer patients are seen as a very vulnerable group [2]. As many studies have shown that patients with cancer have a higher risk of severe clinical events than those without cancer.However, many of the critical issues regarding treatment principles for cancer patients with COVID-19 remain unclear [3]. Trace minerals, especially zn (Zn), have a very prominent role in various physiological and pathological aspects, which has been proven widely in recent years [4]. Zinc is an essential component that plays important roles in various biochemical reactions in many biological systems [5] such as its role as an anti-oxidant due to its being an cofactors of the superoxide dismutase (SOD) enzyme, this enzyme plays an important role in protecting the organism from oxidative stress, thus preventing the onset and development of tumor events [6]. Oxidative stress is implicated as a pathophysiological mechanism of different diseases and is a topic of growing interest [7]. The importance of zinc in biological processes is explained by the idea that its deficiency may play an important role in cellular imbalance, including the development and /or development of cancer [8]. A central clinical feature of zinc deficiency is the increased susceptibility to infectious diseases. This led researchers to speculate that zinc must be important for host immunity [9]. We aim, through this research, to highlight the importance of zinc for cancer, as a preventive treatment against corona infection, and this is in the absence of any clear and specific treatment course.

COVID-19 infection and cancer diseases

Cancer patients are more likely to develop COVID-19 than individuals without cancer due to their immunosuppressive condition caused by malignant tumors [10]. Moreover, cancer treatments such as chemotherapy, radiotherapy, and surgery are factors that inhibit the immunity of patients with cancer who are at

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risk of developing an COVID-19 epidemic viral more than others [11]. Which proves that patients with cancer are susceptible to infection with viruses, a study completed during the influenza A (H1N1) pandemic of 2009, where the results confirm that patients with cancer have cases of pneumonia by (66%) more than others, and that the death rate among patients Cancer was higher (18.5%) after 30 days compared to the general population [12]. One of the mechanisms of immune response against COVID19 is the cytokine release syndrome (CRS) which seems to affect patients with severe conditions [13]. Since lymphocytopenia is often seen in severe COVID-19 patients, the CRS caused by SARS-CoV-2 virus has to be mediated by leukocytes other than T cells, as in patients receiving CAR-T therapy; a high WBC-count is common, suggesting it, in association with lymphocytopenia, as a differential diagnostic criterion for COVID-19 [14]. In light of the pandemic of COVID-19, which overcame the health systems of countries, which threatens the health of cancer patients from two sides, either in terms of postponing treatment appointments, which is a risk to patients and increases the development of the disease [15], or either cancer patients can be called to hospitals and here the risk of infection and infection with COVID-19 increases [16].

Role of zinc in immune system

Zinc is vital for normal development and function of cells mediating innate immunity, NK cells and neutrophils [17]. Zinc deficiency affects multiple aspects of the immune system, from the barrier of the skin to gene regulation within lymphocytes [18]. The importance of zinc for proper immune function is best observed in zinc-deficient individuals. Zinc deficiency affects Phagocytosis, intracellular killing, and cytokine production and also the growth and function of T and B cells [19]. The development of acquired immunity is affected also by zinc deficiency through preventing both the outgrowth and certain functions of T lymphocytes such as activation, Th1 cytokine production, and B lymphocyte help [20]. Likewise, B lymphocyte development and antibody production, particularly immunoglobulin G, is compromised. Zinc deficiency adversely affects the macrophage, which a pivotal cell in many immunologic functions, which can dysregulate intracellular killing, cytokine production, and phagocytosis [21]. Patients with zinc deficiency show symptoms in the immune system such as a decline in the number of lymphocytes, especially helper T cells with an increase in cytotoxic T cells and monocyte cytotoxicity, with reduced activity of natural killer (NK) cell [22]. The immunologic mechanisms whereby zinc modulates increased susceptibility to infection have been studied for several decades. The influence of zinc on viral infections depends on zinc status at baseline measurement, zinc supplementation concentration and frequency, zinc species and age [23].

Zinc in cancer disease

Since many studies focus on the causes and treatment of breast cancer, but still many important and unknown elements have a role in this disease [24], including the role of trace elements that play important roles in biological processes related to breast cancer, including zinc, which is a very important component that is active as an element [25]. It is essential in activating many of the enzymes involved in the synthesis of DNA and RNA, where many studies indicate that low levels of zinc in the blood are diagnosed for many malignant diseases, including cancerous diseases [26]. Zinc has been implicated in mediating apoptotic cell death. Both indirect and direct apoptotic effects of zinc have been demonstrated in cancerous cells [27], which illustrate that zinc active cell growth arrest at G2/M according to the dose used. zinc has been attributed also in inducing the expression of p21, a cyclin-dependant kinase inhibitor known to govern cell progression at this phase [28]. Changes in blood zinc has been found in lymphoproliferative disorders as well as in breast, lung and gastrointestinal tumors [29]. Research indicates that the concentrations of zinc in the serum or plasma are low in people with cancer [30], which is consistent with severals study, which confirms that there is a strong relationship between low levels of zinc and cancer [31-32].

Predictable effects of zinc supplementation

It has been proven that zinc deficiency is the cause of many imbalances in the body in terms of slowed growth or susceptibility to disease, through many studies conducted on humans and animals [33], but a zinc supplement can correct these imbalances and is also useful for resistance against severe recidivistic infections or aging disease [34]. Zinc has been shown to have important therapeutic effects, such as its role in acute diarrhea, intestinal dermatitis [35] and its therapeutic role against aging diseases such as prevention of blindness in patients with macular degeneration as well as its role in relieving colds [36]. Zinc also enhances the up-regulation of A20 mRNA in HL-60 cells (promyelocytic leukemia cell line), which decreases NF-κB activation, IL-1β and and IL-8 leading to decreased gene expression and generation of tumor necrosis factor-α (TNF-α) [37]. On the other hand, zinc supplementation in young people and the elderly is very important in reducing oxidative stress and generating inflammatory cytokines, which allows the prevention of several diseases [38]. Also, zinc supplementation works to reduce vascular generation and induce inflammatory cytokines, which reflects the beneficial effects of zinc against cancers [39]. It has been clinically discovered that zinc supplementation has a primary role in inhibiting rhinovirus 3C protease and viral replication [40].

Therapeutic doses of zinc

The total zinc content in the human body amounts to 2–4 g, with a plasma concentration of 12–16 μM [41]. The average adult requires approximately 8 to 11 mg of zinc per. The use of zinc as a treatment with a studied dose can have a positive effect against chronic and acute viral infections and also can reduce the symptoms associated with this infection [42], either by activating the immune response in patients who suffer from zinc deficiency,

or using a zinc supplement as a protective factor to inhibit viral replication or infection-related symptoms [43]. In a study conducted on rats, it was proven that doubling the zinc ratio five times over the normal value in food reduces the effects of oxidative stress in the testicles caused by diabetes [44]. The use of a zinc supplement at a dose of 10 mg with 6 times / week for 6 months a significant decrease in the prevalence malaria with 22% fewer fever episodes than the placebo group [45]. In a clinical trial conducted on children, it proved that the use of supplemental zinc at a dose of 20 mg / day reduced the duration of their pneumonia, which contributed to reducing the length of their stay in the hospital [46]. On the other hand, a number of researchers confirmed that the use of routine zinc supplements for a period of three months had a positive effect In reducing the severity of infections of the lower respiratory tract in children as well [47]. Also, in another study, it was pointed out that the great benefits of zinc supplements that are taken daily at a dose of 20 mg to prevent infection and reduce viral infections in healthy older adults [48]. Several analyzes of the results of previous studies have shown that oral zinc supplementation reduces the incidence of acute respiratory infections by 35%, reduces the duration of influenza-like symptoms by about two days, and also increases the rates of recovery among patients. Also, several other studies conducted in the United States India, South Africa and Peru demonstrated the positive effect of zinc supplementation, whose dose ranged from 20mg/week to 92mg/day [49-50]. Using a high dose (1 mg / kg) of zinc as a supplement can improve several symptoms such as diarrhea, weight loss, frequent viral and bacterial infection, skin inflammation, hair loss and neuropsychiatric disorders [51]. On the other hand, common cold symptoms can be reduced by taking zinc supplements at a dose of more than 75 mg / day in healthy people [52]. However, excessive use of zinc has undesirable effects such as low copper level, low iron function, red blood cell abnormalities, decreased neutrophils and decreased immune function by consuming zinc for long periods at doses ranging from 50-150 mg / day [53].

In conclusion, with the multiple doses approved from zinc, we suggest that there be an supplement in zinc by 50 mg / day for three month with each treatment for cancer patients, in order to strengthen the immune system to prevent the serious effects of COVID19 infection.

Conflicts of Interest

The authors declare no conflicts of interest.

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PERSPECTIVE

The Tale of Two C's, Cancer and COVID-19: Oncologist's Viewpoint from India

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Abstract

Cancer as a malady is perspicacious and molds itself just before we reach to stab it, on the other hand, COVID-19, an entity with limited genetic material is affecting entire humanity in such a florid way is overwhelming and the mechanism is so simple yet so authoritative. COVID-19 pandemic is affecting all dimensions of mankind with maximum impact on the healthcare system and economy. We the oncologists are so constrained and helpless due to a blooming pandemic, which we have never seen in recent history. We wish to highlight certain issues pertaining to cancer care, which became relevant in such vacillating anticipation. Another dimension needs consideration for limited resources countries; they will always be in the state of prolonged waitlists, limited availability of quality care centers, and hence inferior cancer outcome. Closing the machinery of radiotherapy, surgical and medical oncologists sitting idle is a big loss for sure. We here discuss and suggest a few need of the hour interventions.

Keywords: COVID-19- Cancer care- India

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Introduction

Cancer as a malady is perspicacious and molds itself just before we reach to stab it. Such excellent harmony amongst cells and their microenvironment is beautiful to witness, yet annoying for a clinician and scientist. On the other hand, COVID-19, an entity with limited genetic material (ss, + sense RNA 26-32kb) can affect entire humanity in such a florid way is overwhelming and the mechanism is so simple yet so authoritative [1]. The difference here is that probably we could have prevented such zoonotic infections killing humans, but that is not always possible with cancer. However, cancer is known since antiquity but remains an indecipherable entity because it has complex pathogenesis, requires complex treatment and shows a complex outcome. These patients are a unique set of population, needs specialized, multimodality and prolonged control care.

Coronavirus discovered in 1965 (Strain B814) responsible for the insipid common cold to humans and kept the reputation of submissive human pathogen until 2002, when SARS-CoV presented as pandemic, responsible for nearly 8000 infections and 800 deaths across 29 countries and responsible strain was animal pathogen, which evolve capabilities for human transmission by loco regional gastronomy and culture. India had reported three such cases but no death. Another Epidemic of MERS-CoV (Middle East respiratory syndrome; Camel Flu) is worth mentioning, it started in 2012 and continuing in low frequency, with nearly 2500 cases and 866 deaths across the globe. Most recently in line is the COVID-19 pandemic, which started in December 2019 in Wuhan city of China, attributed to SARS-CoV 2.0. This is more florid than two earlier events and declared as a pandemic in March 2020 by WHO, as of now, more than 190 countries have reported more 3.5 million confirmed cases with about 2.5 lakh deaths by 7 May 2020. This reinforces the fact that yet again, we are far from perfect [2].

India's Response

COVID-19 pandemic is affecting all dimensions of mankind with maximum impact on the healthcare system

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and economy. In response to the COVID-19 pandemic, the Government of India acted and imposed complete lock down for 7 weeks from 25 March 2020, which later modified as selective lockdown, to check the rambunctious expansion, and proven fairly successful. The Ministry of Health and Family welfare rose to the occasion and ensured prompt capacity building, training for health care and collaborating with the public and private sector. Indian Council of Medical Research advised COVID-19 testing for all symptomatic individuals returning from international travel in preceding 2 weeks, all symptomatic exposed health care workers and asymptomatic individual having a history of close contact with a confirmed case [3]. Currently, 132 public and 52 private centres are offering COVID-19 testing using RT-PCR on the throat and nasal swab. Board of Governors Medical Council of India issued telemedicine guidelines to facilitate and maintain patient care amid this pandemic. Online teaching for nurses and doctors using online video platforms is being practiced and promoted [3].

Oncologist's trepidation

We the oncologists are so constrained and helpless due to a blooming pandemic. We wish to highlight certain issues pertaining to cancer care, which became relevant in such vacillating anticipation. Recent publications from China with small size, retrospective experiences, have reported the impact of COVID-19 on cancer. But susceptibility for mortality associated with COVID-19 for cancer patients, beyond age and other comorbidities is not well established yet. University of Wuhan Hospital study concluded that cancer patients are twice at the risk of getting affected with COVID-19. Liang et al. reported the rate of hospital-acquired COVID-19 was up to 41% in, while it was reported to be 28.6 % in specialized cancer hospitals by Yu J et al. Among the COVID-19 cancer cohort, 35 % were advanced cancers, 70% of those had a fulminant course. Rate of COVID-19 infection in cancer patients was higher than community level (OR, 2.31; 95% CI, 1.89-3.02), but that is due to higher admission and hospital stay in those patients [4-5]. COVID-19 has a contagion metric (R0) of 2-2.5, but natural history yet to be deciphered. The first case in India was reported on 30 January 2020, and cases are increasing gradually, despite mitigation efforts and lockdown. As per current predictions, we expect it will remain for the next 3 to 4 months. So, it is not going to settle soon hence health care providers must learn to work with raincoats in corona rain [6].

Data on Cancer's contribution to total OPD and IPD patient load in India is not clear but it is substantial and requires significant infrastructure & man-hours of health care workers. As per WHO reports, cancer is responsible for about six percent of total deaths in India, which is lesser than global data of 13% [7]. 70% of global cancer deaths are reported from low middle-income countries (LMIC). Any cancer patient eligible for curative-intent treatment is quasi-emergency and expectant management is detrimental for most of the cancers. Delaying cancer treatment for more than one month adversely affects the survival across all stages [8]. How much time one can wait safely is not possible/ethical to find, we cannot generate literature on that. The desirable time to initiate cancer treatment is not based on evidence but logistics. As per NHS, cancer treatment should be started within 62 days of diagnosis. In India, we do not have such guidelines. If a patient has an acute cardiac event or stroke needs it mandates urgent medical care and lockdown is providing relaxation for that. Patients requiring elective surgery like joint replacement can wait and need not much attention during a pandemic. There are two questions, whether we can give the treatment breaks to these patients and can we offer them something alternative if we accept the break?

An oncologist considers the stage of the disease, cancer biology, performance status, comorbidities, etc. in addition to logistics before designing treatment. Logistics includes the availability of safe, effective, and prompt treatment. Logistics have the highest impact on the outcome though least studied aspect. Patients in early-stage conditions need to be dealt with differently as they are potentially curable. For advanced disease, despite prompt and effective treatment, they might not benefit a lot. There are different guidelines, based on COVID-19 burden, government policies on restriction, epidemiological factors, and availability of resources in addition to cancer and patient-related factors. Access to healthcare for cancer patients is difficult in the current restrictive mobilization state, as public transportation is seized and travel for such patients is a major issue.

Precision medicine in COVID-19 Storm

The alternative for such unplanned gap cannot be explored with strong study designs. For hormone-positive breast, hormonal therapy is probably the most effective option for stages of the disease, but such alternative options are missing for many clinical scenarios. Alternative oral drugs like Capecitabine, Cyclophosphamide, or Etoposide are options but inferior choices. Balancing this is a cumbersome task. Another dimension needs consideration for limited resources countries; they will always be in the state of prolonged waitlists, limited availability of quality care centers, and hence inferior cancer outcome. Closing the machinery of radiotherapy, surgical and medical oncologists sitting idle is a big loss for sure. A country with more than seven lakh, annual death due to cancer cannot afford to waste limited resources. Moreover, it is frightening to imagine the struggling health care, if we postpone everything for later. We are proposing our essential recommendation based on local needs, some specific and some-general (Table 1).

Declaration and authorship

Contributions of authors

DRP and AS conceived the research idea and searched the literature.

AS ensured data collection, analysis and interpretation.

Manuscript written by DRP and AS.

Manuscript and facts were reviewed by MKG.

Table 1. Precision Medicine in COVID-19 Storm

Domains	Recommendations
Administration	● Working hours: Identify the burnout of HCWs, keep them motivated, and appraise them regularly about evolving scenarios and road ahead.
	● Psychological Support: Strategies to uplift the morale HCWs are vital in this battle, so the development of a psychological support team is indispensable.
	● Detached, discrete & distinct cancer care: Separate wing/area for cancer care, away from COVID-19 care with well-planned protocols for screening and dedicated quarantine policies for Cancer patients.
	● Allied specialty: Cancer provider from allied specialty (Pathology/radiology/ dietetics/anesthetist) needs to be identified and dedicated to cancer care only.
Human Resources	● Their protection with appropriate training, equipment availability, PPEs, timely work segregation, and quarantine are the key steps.
	● They need to be work in planned teams specific for oncology subspecialties for a defined period.
	● They can switch their roles periodically to maintain a continuum of care for cancer patients.
Non-Human Resource	● Blood products, neutropenic isolation rooms, and PPEs need to be allocated with almost care.
	● All Cancer care units need to be ready with a contingency plan according to their local resources and needs.
	● Approach for drafting workflows and policies shall be adaptable for local needs and day-to-day evolving scenarios, which is critically important for pandemics management planning.
	● PPEs and Masks strategy to be devised specifically to a clinical setting. Routine cancer care to be provided using a surgical mask and meticulous hand hygiene and N-95 respirators/PPEs to be reserved only for COVID-19 areas or neutropenic units of oncology.
General Mitigation Policies	● Social distancing, avoiding unnecessary travel and limiting crowding is most crucial for fighting COVID-19 or any other similar pandemics
	● Both OPD, as well as IPD visits, need to be curtailed with only one care provider permitted with the patient.
	● Routine follow-up visits to be suspended for the next 8-12 weeks.
	● Administrative staff needs to be sensitive and motivated enough to identify the burnout of HCWs, keep them motivated, appraise them regularly about evolving scenario and road ahead. Strategies to uplift the morale of HCWs are vital in this battle.
	● No Group meetings to be allowed
Patients care	● Information for patients: National wide awareness for each individual and potential harms should be readily available.
	● Personalized care: Every Cancer patient is having a unique clinical situation and requires evaluation on a case-to-case basis with the participation of all stakeholders including care providers, allaying their concerns about consequences of continuing or interrupting the cancer-directed therapy.
	● New Patients: Timely labeling the intent of treatment (Curative or palliative), curative patients should be offered care promptly. Palliative patients with acute emergency provide prompt care.
	● Potentially curable patients with indolent disease biology- can wait with appropriate counseling.
	● Adjuvant Care: care should not be delayed. The treating physician shall identify, the best action plan for the patient individually and ensure delivery. Telemedicine, video consultations and advice to second-tier centers should be encouraged.
	● Palliative treatments beyond first-line with limited impact on cancer outcomes can be delayed, this will also reduce the burden on health care system with limited resources like India.
	● Maintenance chemotherapy patients can also be put on a lower priority list and such treatments can be discontinued with informed decision-making process.
Training & capacity building	● Use of appropriate technology can prove very important. Services like telemedicine, videoconferencing, WhatsApp, email and telephonic consultations will reduce unnecessary exposure events while maintaining basic care for the needy.
	● Separate OPD for cancer patients after COVID-19 screening (Fever/Cough/Breathing difficulty with History of exposure) and timely disposal.
	● Segregation of entry of HCWs and patients' health care facilities to be planned to further strengthen social distancing an avoiding unintended exposure.
Collaboration & Research	● Cancer corona consortium reporting for cases.
	● Cancer research should be continued, without break.
	● COVID-19 research is promoted by Govt. of India, shall be encouraged and appreciated.
Teaching	● Involvement of Medical and Nursng graduates for capacity building and training to do basic supportive or clinical work
	● Classical methods of teaching and lectures to be suspended
	● Teleconferencing for academic classes or COVID-19 training to be promoted
	● Practical training must strictly follow the rules of social distancing
Future	● Focus on continuous capacity building for any such eventualities in the future and draft effective policy.

Conflict of Interest

Authors declare no conflict of interest

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PERSPECTIVE

How We Treat Genitourinary Cancers During COVID-19 Pandemic?

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Abstract

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) has become a pandemic and affected the entire globe. Daily routine life is affected due to global restriction of movement and infected more than 3.7 million peoples in more than 200 countries. It's an invisible enemy which has imposed a clear threat to the humanity. Patients other than COVID-19 is also suffering a lot due to this unforeseen circumstances. This pandemic also shaken the powerful nations with best of healthcare settings. Oncology is a unique sector of healthcare as cancer patients are at more risk of SARS-CoV-2 infection and cancer treatments are also affected. Many regulatory bodies and professional organizations have come up with guidelines for healthcare personals and patients to guide anti-cancer treatment during COVID-19 pandemic. It's time to formulate local treatment guidelines to guide cancer treatment with optimum use of healthcare resources at society and national level keeping in mind the load of COVID-19 at the concerned region. We have formulated guidelines to manage genitourinary cancer patients during this pandemic, especially in resource constraint setting with the aim of – optimum treatment of these patients with reduction of risk of contracting SARS-CoV-2 infection without affecting oncological outcome.

Keywords: SARS-CoV-2- gentourinary- COVID-19- guidelines- cancer

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Introduction

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) has become a pandemic and posed a great threat to humanity. With over 200 countries affected by the pandemic, more than 3.7 million infected cases, and deaths exceeding 250,000 as on 8th May 2020 [1], the impact of COVID-19 pandemic is enormous in terms of loss of human lives and financial disruption, which is leading to loss of employment.

Cancer patients are at an increased risk of acquiring the infection, requiring ventilator support and a higher risk of death. Patients who received chemotherapy or underwent surgery in a month before acquiring SARS-CoV-2 infection were at high risk of an adverse outcome [2-3]. Thus, the scenario in oncology is unique and patients with cancer are facing a clear danger during the COVID-19 pandemic. There are increased chances of disease recurrence due to delay in anti-cancer treatment.

The oncologists face the following situations in clinical practice -a) Patient with cancer and symptomatic SARS-CoV-2 infection; b) Cancer patients tested positive for SARS-CoV-2 in contact screening, but asymptomatic and c) Asymptomatic cancer patient with undetermined SARS-CoV-2 status. Patients in oncology outpatient clinics can be from the following categories - a) those who are under evaluation for suspected cancer or recently diagnosed with cancer, b) those who are already on active anticancer treatment, c) those who are on follow-up after completion of active anticancer treatment. Further, the underlying cancer can be either localized or locally

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advanced where intention of treatment is cure or metastatic disease where intention of treatment is palliative. The questions that needs to be addressed while treating patients with genitourinary cancers (GUC) during this pandemic are -

(1) Localized disease –Whom to treat now and for whom treatment can be deferred without compromising the oncological outcomes? Is anti-cancer treatment safe during this pandemic? And can alternative strategy act as a bridge to the deferred curative therapy?

(2) Metastatic disease: Who should be treated without delay and whose treatment can be deferred? How much treatment is safe and optimal? Any alternative safe approach e.g. less toxic but effective?

(3) How to consult patients who are on follow up and to minimize their hospital visits.

We formulated a guideline for management of GUC patients during the current COVID-19 pandemic with the primary aim of providing optimum cancer treatment during the current country-wide lockdown without compromising oncological outcomes and minimizing risk of SARS -CoV-2 infection to our patients and health care staff.

Urothelial tract cancers

Superficial bladder cancer

Most of the patients (75 %) with bladder cancer present as superficial bladder tumors. High grade non-muscle invasive cancer can be treated with trans-urethral resection of bladder tumor [TURBT] +/- intravesical BCG and cystoscopy surveillance. Patients with low-grade superficial bladder tumors can be treated with a single dose of immediate intravesical gemcitabine after TURBT [4]. The risk of getting SARS-CoV-2 infection is much higher than the benefit of intravesical BCG if a patient has to attend a health care facility frequently.

Muscle invasive bladder cancer/upper urothelial tract cancers

Cisplatin based neoadjuvant chemotherapy (NACT) followed by radical cystectomy is the standard treatment for muscle invasive bladder cancer in cisplatin eligible patients. Gemcitabine- cisplatin [GC] should be considered as the regimen of choice due to lesser toxicity and similar efficacy [5], despite absence of a phase 3 randomized control trial [RCT] over MVAC (Methotrexate, vinblastine, doxorubicin, cisplatin) and dose dense MVAC (ddMVAC).

Prior studies (before the NACT era) have shown that delaying bladder cancer surgeries by a few weeks is detrimental and may lead to worse outcomes [6]. But during this pandemic, it may be worthwhile to defer surgery for 4-6 weeks for relatively asymptomatic patients and those with incidental diagnosis. A phase III RCT suggested that delaying chemotherapy till relapse did not result in worse survival as compared to immediate chemotherapy post-cystectomy [7]. For patients who underwent upfront surgery and have pT3 /pT4, N0 or N1 disease, adjuvant chemotherapy can be deferred for at least 90 days without compromising the outcome.

Advanced/metastatic disease

A newly diagnosed patient with suspected metastatic disease will require blood tests to check organ functions and computed tomography (CT) of chest and whole abdomen as baseline staging evaluation. A biopsy or fine needle aspiration is necessary for confirmation of diagnosis before starting treatment. Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1 and who are cisplatin eligible we use 3-weekly gemcitabine (1000 mg/m^2 Day 1 and Day 8) and cisplatin (70 mg/m^2 Day 1 only) regimen with growth factor support, to the patients who can maintain adherence to treatment owing to restriction of movements during this pandemic. This will reduce the hospital visits as compared to recommended gemcitabine-cisplatin 4 weekly cycles wherein gemcitabine is given on D1, D8, D15 and cisplatin is administered on D2. Dose dense MVAC should be avoided in view of higher toxicity and comparable efficacy with the gemcitabine - cisplatin regimen. If possible, day 8 chemotherapy can be given at a community health center to avoid frequent visits. Cisplatin ineligible patients will be offered gemcitabine – carboplatin [8]. Patients with Eastern Cooperative Oncology Group performance status (ECOG PS 2, 3 and 4) should be offered palliative care. Gemcitabine induced lung injury, though rare, can mimic symptoms of COVID -19 and should be kept in mind [9].

Immune check-point inhibitors [ICIs] are approved as first-line treatment in platinum ineligible patients and can be used in patients with high PD-L1 score. It should be clearly discussed that only a few percentage of patients get a prolonged response with anti PD-L1 therapy. Patients who are already on anti PD L1 therapy and have achieved a good response can consider a treatment break and restart therapy upon disease progression or after the pandemic is controlled. Pembrolizumab can be given 400 mg every 6 weeks as per the latest USFDA approval and nivolumab can be given 480 mg every 4 weekly as opposed to routine cycles and thus hospital visits can be reduced by 50%.

Five ICIs are approved in 2nd line treatment of urothelial tract cancer, out of which nivolumab, atezolizumab, durvalumab and pembrolizumab are available in India. However, the benefit is limited to few patients only. ICIs can cause pneumonitis, which might be difficult to differentiate from SARS-CoV-2 infection and treatment of both is drastically different. Patients should be warned of this side effect and upon developing any such symptoms the patient should contact the nearest health care facility immediately. ICIs remain the drug of choice after platinum failure and are relatively well tolerated with few grade 3 or 4 ICIs induced pneumonitis. The third and subsequent line of treatment should be avoided as the standard of care is not available in India and risk-benefit ratio is high for any experimental therapy during this pandemic. If a patient is responding clinically, imaging may be deferred for 3 to 4 cycles.

Prostate Cancer

Prostate cancer is a disease of older adults, who

often have other comorbid conditions. They are at high risk of acquiring SARS-CoV-2 infection and optimum care should be given to them during this pandemic. There are certain subsets of prostate cancer patients where treatment can be delayed or the regimen can be altered without compromising cancer related outcomes.

Localized prostate cancer

Prostate cancer is generally a slowly progressing disease, with low and intermediate risk disease amenable for radical prostatectomy, radical radiotherapy as well as active surveillance, on a case to case basis. The question is - how long can we delay the surgery? Korets et al [10] in their study on 1561 men with localised prostate cancer opting for surgery, concluded that a delay of > 60 days was not associated with any adverse pathological outcomes. Additionally, it did not correlate with worse biochemical recurrence free survival. Therefore, patients can be re-assured that delaying treatment in the current scenario, would not adversely affect their outcomes.

Another clinical dilemma is regarding the surgical approach- whether it should be an open or a minimally invasive surgery? The potential benefits of minimally invasive (robotic/laparoscopic) surgery include lesser blood loss, well visualised operative field, lesser post-operative discomfort and lesser in-hospital stay. However, there have been realistic concerns regarding the risk of dissemination of SARS-CoV-2 during minimally invasive surgery, which is considered an aerosol generating procedure [11]. Particles in surgical smoke have been demonstrated to contain a variety of toxic and virulent materials potentially capable of infecting through inhalation. In a nutshell, a surgical delay for patients with localised prostate cancer may not be very harmful, and if needed- surgery should preferably be performed via an open approach. Adjuvant radiotherapy if indicated can be delayed till recurrence. If radical radiotherapy is planned, then hypofractionation [once weekly x 5-6 weeks] should preferably be used.

Locally advanced prostate cancer

Patients planned for definitive radiotherapy plus androgen deprivation therapy should be started on neoadjuvant ADT. Neoadjuvant ADT may be safely given for 4-6 months. Consider use of 3 or 6 monthly formulations over monthly injection. Hypofractionated external beam radiotherapy should be used and may be delayed up to 6 months.

Metastatic hormone sensitive prostate cancer [mHSPC]

The treatment of mHSPC has witnessed a paradigm shift in the last few years. Androgen deprivation therapy (ADT) alone is the treatment of choice for a minority of mHSPC. ADT with chemotherapy (docetaxel) or androgen receptor (AR) targeted therapy (abiraterone acetate, enzalutamide, apalutamide) is the new standard of care in majority of mHSPC patients [12-13]. Aim of therapy in the present time is to minimize hospital visits without compromising oncological outcomes. For symptomatic patients, use of GnRH antagonist is preferred, which is rapid acting and also minimizes the risk of testosterone flare. Once initiated, patients should be encouraged to take further injections at peripheral centres and follow up 3-4 monthly. For asymptomatic patients, GnRH analogues may be considered, which can be used at 3 or 6 monthly intervals. Surgical castration is better avoided. Interim follow-up can be done by telemedicine.

It is prudent to avoid chemotherapy during this pandemic as there are higher chances of myelosuppression, febrile neutropenia and resultant morbidity. Amongst all available trial results of ADT with other agents in patients with mHSPC, enzalutamide remains the safest and should be first choice during this pandemic followed by abiraterone acetate-prednisolone. Chemotherapy should be considered as the least preferable option and if required, can be delayed up to 4 months [14]. Follow-up intervals should be increased to 2-3 months and patients can be monitored telephonically with local lab tests. Radiological tests should be postponed unless there is some urgent clinical indication like, cord compression or fracture.

Castrate resistant prostate cancer

Various factors including patient's age, comorbidities, ECOG PS, duration of response to prior treatment and disease burden determine the choice of therapy. The available options include chemotherapy (docetaxel, cabazitaxel), AR targeted therapy (abiraterone acetate, Enzalutamide), poly ADP ribose polymerase (PARP) inhibitors (olaparib) for those with germline BRCA/ ATM mutations, and ICIs for those with tumor positive for microsatellite instability. Chemotherapy, olaparib and immunotherapy may be avoided due to associated myelosuppression and immunosuppression. AR targeted therapy should be preferred because they are less toxic, require less frequent monitoring and fewer hospital visits. Patients who have progressed on multiple lines of therapy and are symptomatic should be offered hospice care at a local health facility or oral cyclophosphamide [15]. Bone modifying agents, like - zoledronic acid can be given at 3 monthly intervals.

Renal Cell Cancer (RCC)

Early stage disease

Radical nephrectomy remains the treatment of choice from stage 1 to stage 3 renal cell cancers and should be practiced. Patient can be kept on close observation in small size tumor (<2 cm) or surgery can be delayed for few weeks in relatively asymptomatic patients. Open surgery can be preferred over laparoscopic surgery to avoid aerosol generation. Alternative approach like – radiofrequency ablation or transarterial embolization can be attempted in place of radical surgery in small tumors or those with borderline fitness. Adjuvant use of tyrosine kinase inhibitors [TKI] should be discouraged in view of minimal survival advantage with very high treatment related toxicities.

Metastatic disease- upfront therapy

Last decade has seen a significant change in the

management of metastatic clear cell renal cell cancer (RCC). Vascular endothelial growth factor (VEGF) targeted therapies and very recent ICIs +/- vascular endothelial growth factor (VEGF) targeted therapies have become the new standard first-line therapy for mRCC [16-18]. In addition to systemic imaging, all patients should be assigned a risk category (favourable, intermediate and poor) based on International Metastatic RCC Database Consortium criteria which includes Karnofsky PS, haemoglobin, platelet count, absolute neutrophil count, corrected calcium, and time from diagnosis to systemic therapy.

A recent phase III randomized controlled trial demonstrated that sunitinib alone was not inferior to sunitinib followed by cytoreductive nephrectomy in mRCC. However, there is a role of cytoreductive nephrectomy in a small subset of patients (in those with oligo-metastatic disease, very low burden disease or with indolent course). During the ongoing pandemic, it is prudent to delay cytoreductive nephrectomy.

Either VEGF targeted therapy or ICIs should be considered as the first line therapy in clear cell mRCC. Recent studies have shown pembrolizumab + axitinib, avelumab + axitinib, ipilimumab + nivolumab and bevacizumab + atezolizumab to have superior efficacy to sunitinib. Complete response rates are higher with these agents compared to VEGF targeted agents alone. Specific susceptibility to bacterial or viral infections in patients receiving ICI have not been studied. There is a possibility that patients undergoing ICI based therapy could be more immunocompetent than cancer patients undergoing chemotherapy. Also there is a possibility of cytokine release syndrome with use of ICI which can account for higher COVID-19 related complications [19]. Pembrolizumab can be used 400 mg every 6 weeks and nivolumab can be used 480 mg every 4 weeks as per the latest USFDA recommendation [20]. There can be overlapping features of cytokine storms due to ICI and SARS-Cov-2 infection. Thus, the decision to use ICI over VEGF TKI should be carefully discussed with patients. Use of therapy will require more hospital visits, but has a higher chance of complete response with long-term control. At minimum, for elderly, frail and patients with multiple comorbidities – it may be judicious to use VEGF targeted therapy, while for others, immunotherapy combination / VEGF targeted therapy are the options.

2nd line & subsequent line of therapy

Patients who have progressed on the first line anti VEGF TKI may be treated with nivolumab, lenvatinib + everolimus or axitinib. Another active agent, cabozantinib is not available in India. Among these, axitinib or nivolumab [4 weekly schedule] might be better options because lenvatinib +evverolimus is associated with higher toxicity, and dose reduction is needed in approximately 45% of patients. Further, everolimus is immunosuppressive and can cause interstitial lung disease, mimicking the symptoms of COVID-19.

Testicular germ cell tumors

Testicular germ cell tumors (TGCT) are the most common solid organ cancers in males between the age of 15-40 years. These are highly curable malignancies in all stages. Since the intention of treatment is cure in all stages, it is imperative to adhere to the standard treatment.

Some of the changes / precautions which can be considered in treatment for GCT patients during this period

1. For stage 1 seminoma, instead of active surveillance, a single cycle of carboplatin with Area Under Curve x 7 can be preferred. This will require less frequent hospital visits and will not compromise the efficacy.

2. In advanced stages, avoid etoposide, ifosfamide and cisplatin [VIP] based chemotherapy as it is more myelosuppressive than EP or BEP.

3. Bleomycin toxicity can mimic symptoms of Covid -19. For standard risk and intermediate risk disease, etoposide & cisplatin [EP] should be the treatment of choice. For high risk disease, there is a trade-off between bleomycin, etoposide & cisplatin [BEP] and VIP

In conclusions, the following principles of treatment should be used during treatment of patients with GUC during this COVID -19 pandemic.

1. Delay any treatment whenever feasible if oncological outcome is not compromised.

2. To avoid exposure, minimize hospital visits. Use telecommunication in the form of telephonic consultation or telemedicine.

3. Avoid chemotherapy and immunosuppressive therapy, whenever feasible. Try to find an alternative.

4. Shortest duration external beam radiotherapy regimen may preferably be used for prostatic RT.

5. For patients receiving oral targeted therapies, lab tests can be done at local labs and can be consulted on telephone or telemedicine.

6. Targeted therapy is safer and should be preferred over chemotherapy during COVID-19 pandemic.

7. Surgery may be delayed whenever possible.

8. Open approach instead of minimally invasive surgery should be preferred.

9. Germ cell tumors should not be denied chemotherapy due to high cure rates.

10. Clinic based routine follow-up should be discouraged.

11. Prophylactic growth factors should be used liberally with chemotherapy.

12. Radiological response assessment preferably delayed if there is a clinical response.

13. Screening & enrolment in clinical trials should be carefully executed during this pandemic if the patient (s) can maintain adherence to the protocol and in close & constant collaboration of the study team, sponsor and the ethics committee.

14. All patients & health care staff should follow the universal precautions laid down by local & national health authorities to prevent contracting SARS-CoV-2 infection.

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PERSPECTIVE

A Practical Guide to Mitigate the Response of Corona Virus Pandemic in Radiotherapy Treatment

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Abstract

The current global pandemic of Corona virus has impacted the health care severely. Many of the non-emergency cases and general illness cases have been asked to avoid hospital visit or wait for elective surgeries. The same may not be possible for the patients suffering from cancer as it considered a major health problem owing to the risk of metastasis as well as disease becoming unresectable with time. Unfortunately, we don't have studies weighing the risk versus benefit ratio of delaying oncological treatment weighted against an added comorbidity of COVID infection. Radiotherapy being an integral part of cancer care is affected the most as it is delivered, continuous over a long period of time and unplanned gap because of travel restriction on patients makes decision making more difficult for radiation oncologist. In this article we've highlighted few major problems in delivering radiation to cancer patients at this time of global pandemic of corona virus and tried to find out possible solution.

Keywords: Radiotherapy- COVID-19- corona virus

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Introduction

In December, 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia [1]. Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named 2019 novel coronavirus (2019-nCoV). On January 30, the World Health Organization has declared the coronavirus outbreak a global Public health emergency. Till date more than ten lakh people have been infected worldwide and more than fifty thousand lost their lives because of this viral infection [2]. Common symptoms of COVID-19 are, fever, cough, myalgia or fatigue, less common features are, sputum production, headache, hemoptysis and diarrhea [3]. The disease can spread from person to person through small droplets from the nose or mouth which spreads when a person with COVID-19 coughs or exhales, hence social distancing and avoiding social gathering may protect us from acquiring this infection [4]. Self-initiated quarantine for 14 days by people with mild symptoms remains most important public health intervention, but testing of all suspected cases, symptomatic contacts of probable and suspected cases, would still be required.

Cancer patients are more likely to get COVID-19 infection as they are immunosuppressive because of cancer itself or cancer directed treatment i.e. radiotherapy, chemotherapy, immunotherapy or targeted therapy.

To contain the spread of COVID-19, government has closed public places, public transport and also imposed laws to prevent social gatherings because of which it's difficult for patient to visit Radiotherapy facility daily for the treatment. Many questions appear in front of radiation oncologist, which makes decision making more crucial as no standard guidelines exists, most important being; in which patients' radiotherapy can be avoided or delayed, dose adjustment for unplanned treatment gaps during radiation therapy, how to prioritize new cases to offer maximal benefit by starting radiotherapy early and how to manage a patient infected with COVID-19 during or before radiotherapy.

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Practical approach

The ultimate dilemma to offer or avoid radiotherapy

Patient expected to derive maximum benefit by radiotherapy should not be deprived of treatment. In cases where radiotherapy has no survival benefit and only decreases locoregional recurrence it may be avoided. Braunstein et al. and Simcock et al. [5-6] has recently published their views, mentioning site directed subset of patients in which radiotherapy can be avoided. Breast cancer patients who underwent breast conservation surgery and have DCIS (Ductal Carcinoma in Situ)/ low risk invasive disease in older patients/ invasive disease with low risk genomic profile or underwent mastectomy and have T1-2, N1 disease, radiotherapy can be omitted in this group of patients. Prophylactic cranial irradiation can be omitted in small cell lung cancer patients or in patients of non-small cell lung cancer with asymptomatic brain metastasis, whole brain RT can be omitted. Low risk and favorable intermediate risk prostate cancer patients can be kept on active surveillance and radiotherapy can be omitted in oligometastatic disease. Resectable/unresectable stomach cancers, radiotherapy can be avoided. In CNS (Central Nervous System) tumors radiotherapy can be omitted in, old age patient (>60 years) methylated Glioblastoma, Low grade Glioma and in asymptomatic Grade 1-2 Meningiomas [5-6]. Although enough data exists for avoiding radiation in these subsets of patients mentioned above, a careful discussion in multidisciplinary tumor board discussion is recommended.

Can we delay radiotherapy?

As per tumor biology, cancer with slow growth rate or long tumor doubling time, treatment can be delayed without fear of disease getting upstaged. As published by Simcock et al and Braunstein et al, radiotherapy can be delayed in following subset of patients; breast cancer patients who underwent breast conservation and are stage T1-2, N0, luminal A+B, can wait for radiotherapy for up to 12-20 weeks after chemotherapy. In CNS tumors, radiotherapy patients with asymptomatic meningioma WHO grade1, post-op gross total resection and WHO grade 1-2. Prostate cancer patients with unfavorable intermediate, high, very high-risk patients' radiotherapy can be delayed up to 6-7 months by using neoadjuvant hormonal therapy. Basal cell carcinoma of skin can wait for radiotherapy as it is slow growing. In palliative settings, painful metastases without impending structural/ neurological compromise can be treated with pain medications and radiotherapy can be delayed [5-6].

Managing treatment gap

Due to lockdown in various countries globally, it's not possible for one to receive radiotherapy daily or sometimes for a longer interval beyond 7 days. Patients may be unable to receive some fractions in between treatment resulting in prolongation of treatment time or may discontinue their treatment before the completion of prescribed radiotherapy dose. In these patients after weighing risk and benefit of delivering remaining radiation they may be advised accordingly. The paper by Gay et al. [6] evaluating the impact of hurricane Maria in Puerto Rico in 2017, provides guidelines on how to handle treatment interruptions for common disease sites and can be used effectively in present scenario. In breast patients the impact of gap is usually low and patients can be successfully treated with the intended dose as planned earlier. In prostate cancer patients the impact of treatment gap is very low and can be successfully taken for completion of planned radiotherapy dose after a gap. In Head and neck, Uterine Cervix, Small cell and Non-small cell Lung cancer the impact of radiotherapy gap is usually high and treatment should be resumed a soon as possible, and the gap duration should be taken in account while re-calculating the dose to be prescribed [6]. Gay et al. has described site wise treatment approach after treatment gap and we advise to go through the detail paper for those interested [7].

Prioritizing radiotherapy treatment

With the available literature it may be easier to segregate patients in two groups; first, requiring urgent radiotherapy, second, radiotherapy can be avoided or delayed. Radical radiotherapy or chemoradiotherapy with curative intent should be started in patients having rapidly proliferating tumor or treatment has already been started and the impact of treatment gap is very high. It is important to ensure that these patients complete the radiation by providing indoor admissions, dedicated patient quarters or lodge or by providing pick up and drop facility from the place of staying wherever possible. Short course radiotherapy (e.g. rectal cancers) [8] or hypo fractionated radiotherapy protocols (e.g. breast, prostate cancers, Larynx) [9-10-11] should be considered. Overall treatment time reduction without compromising the results may also help in accommodating more patients in a short span of time.

Use of alternative options

Patients in whom radiation is avoided or delayed should be considered for alternative treatment options. Various alternative cancer directed therapy like chemotherapy, hormonal therapy, immunotherapy may be utilized to give benefits to patients. Use of metronomic chemotherapy may be beneficial in patients waiting to be operated or waiting for radiotherapy [12].

Treating COVID-19 positive or suspected cases

WHO has issued guidelines for prevention of spread of COVID-19, hence Priority should be given for recovery from COVID-19, by keeping the patient in isolation for necessary period and radiotherapy should be considered as soon patient turns negative from COVID-19 [4]. Radiotherapy treatment without increasing risk of spread is possible if we judiciously categorize patients. Patients with infective symptoms, but tested negative for COVID-19, may be allowed to continue treatment with adequate protective and safety measures. In patients with suspected or proven COVID-19 infection and who are symptomatic treatment may be deferred until resolution or till they are deemed non-contagious by local health bodies. Patients

with suspected or proven COVID-19 infection but who are asymptomatic may also be deferred treatment until their resolution or till they are deemed non-contagious by local health bodies. In selected patients (successfully treated or asymptomatic) requiring prompt initiation or continuation of radiotherapy, treatment may be allowed after observing all the necessary precautions. A careful evaluation of general health and tolerability of patients for radiotherapy after COVID- 19 infection resolution is must in all cases.

Patient and relatives

Cancer still exists as a major fear amongst Indian population. It is very much emotional and psychological burden for the patients and family members. It is very pertinent to sit together and discuss the pros and cons of avoiding and delaying the radiotherapy and its overall impact on disease control and survival with patients and their family members. In scenarios, where patients relative persuade to start treatment irrespective of benefit it carries, creates an unwanted pressure towards medical resources and care givers in hospital. In present crisis taking help of psychologists and counselors should be considered in these situations and use of electronic media like telephone or video conferencing can be considered if required.

Protection of Radiation oncologists and Staff

Fear of contacting the infection and chances of being caught into a medicolegal controversy during management of these cases are highly possible. Although many guidelines and advisory are [13-14] available for the use of PPE's (Personal Protection Equipment) and safety measures, the psychological aspect of caregivers is often overlooked. Support system of care givers is equally important as that of patients. Medical professional liability insurance of health professional should be considered either individually or through hospital.

Guidelines

Although no set guidelines are available for radiation therapy in COVID-19 pandemic scenario, we have tried to set a practical protocol-based approach. The practical flow chart (Figure 1) may be used to consider radiotherapy in this present crisis. Although this is just a suggestion a careful consideration of patient's disease, COVID status, co morbidities and support of other medical specialities including medical, renal cardiac experts should be taken by the multidisciplinary team before taking a final call.

In conclusion, our Practical flow chart may provide a basic algorithm for categorising patients, depending on various malignancy parameters and help in prioritising radiotherapy treatment in cancer patients, at present scenario of COVID-19 pandemic. Cancer centres are advised to consider these options after careful evaluation of every case and as per expertise available at each centre.

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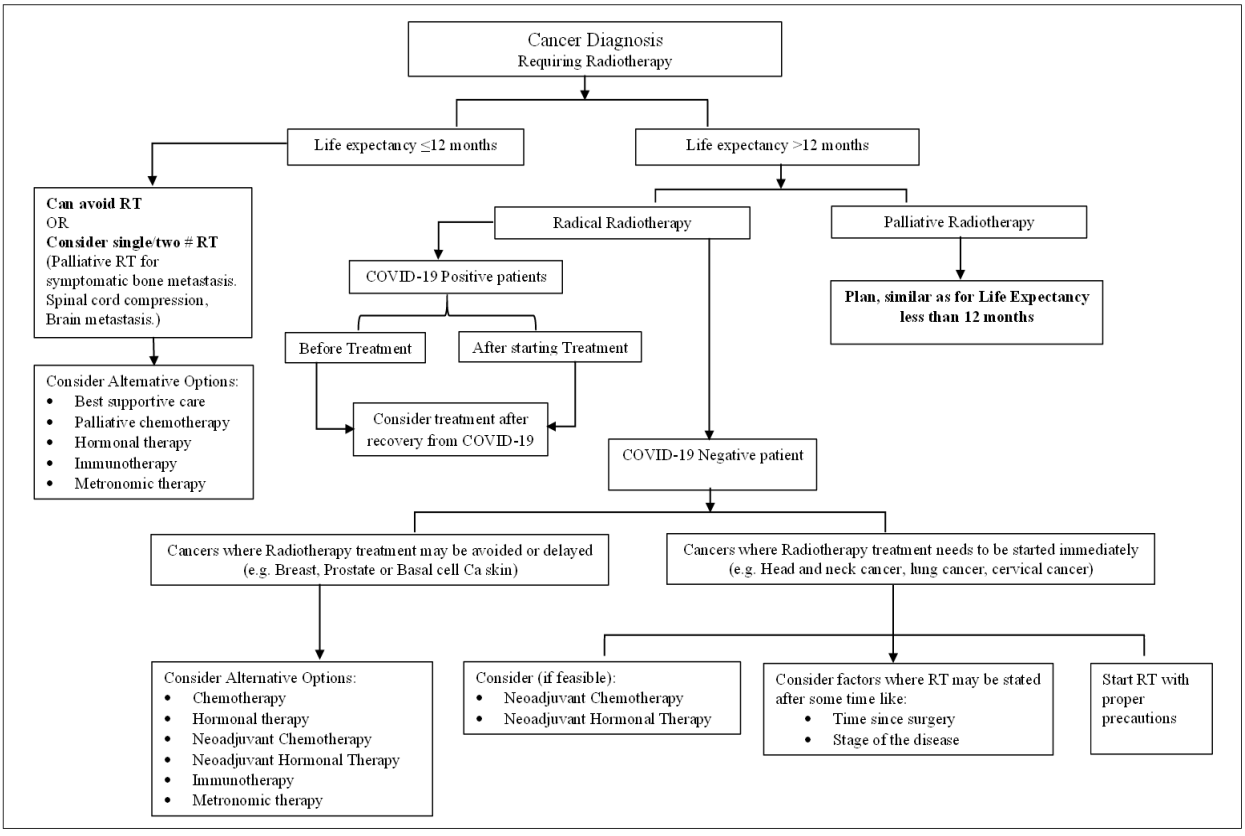

Figure 1. Practical Flowchart

services in the situation of pandemic.

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PERSPECTIVE

Radiotherapy as a Cure for Covid-19 Pneumonia: Is this a Possibility?

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Abstract

The ongoing pandemic of COVID-19 caused by the Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) has affected the healthcare system worldwide to a great extent. Millions of people have succumbed to the disease which might vary from mild febrile illness to severe Acute Lung Injury ultimately resulting in ARDS (Acute Respiratory Distress Syndrome). The mechanism of lung pathology due to SARS CoV-2 infection though unclear, is thought to be due to an imbalance in the inflammatory cascade; leading to a condition called Chemokine Release Syndrome. Low dose Radiotherapy which was historically used to treat Pneumonia, can serve as an approach for this subset of patients; by virtue of its anti-inflammatory response. Thus, in the present time, where a perfect cure is yet to derived all possible interventions should be looked upon with a ray of hope.

Keywords: SARS-CoV-2-COVID-19-Pneumonia-Radiation Therapy

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Introduction

The COVID-19 pandemic has paralysed the health care system of the world, by affecting millions of people till date. It is caused by the Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2). A spectrum of symptoms can be attributed to it, starting from mild flu-like symptoms to severe lung injury or Pneumonia [1]. Approximately 20% of patients progress to ARDS ,which often results in death [2].

Immune mechanism involved

SARS-CoV infection activates both the innate and adaptive immune mechanism .In response to the infection, macrophages release various pro-inflammatory cytokines like IL 1,IL 6, TNF α,TGF β etc leading to a condition called Cytokine Release Syndrome [3]. In addition the infected alveolar epithelial cells also produce various Chemokines like CCL 2,CXCL-10, CXCL-9 [4]. This dysregulated release of cytokines and chemokines cause an imbalance in the immune mechanism, thus playing a role in the pathogenesis of the disease.

This again results in enhanced endothelial and epithelial cell apoptosis, increased vascular leakage, suboptimal response to anti-body and decreased virus clearance [5-6].

Importance of Radiation and its role in Pneumonia

Radiation induces cell death by destruction of DNA either directly or indirectly by production of free radicals (ions) inside the body. Historically, X-rays have been used to treat cancer since Emil Herman Grubbe treated the first patient in 1896. Benign intracranial tumours (e.g. Schwannoma, Craniopharyngioma etc), Glomus tumors, Juvenile Nasopharyngeal Angiofibroma and many other benign tumors are also treated by radiotherapy. Interestingly, there are reports of use of low dose radiation treatment in many acute inflammatory processes and infectious diseases such as gas gangrene, carbuncles, sinusitis, arthritis and mastitis in the pre-antibiotic era with significant cure rates. Even today, low dose radiation is prescribed for benign painful chronic inflammatory degenerative disorders such as periarthritis in Germany. Experiments over past three decades have revealed a multilevel interrelationship between low-dose ionizing radiation and inflammatory cascades which include:

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modulation of the inflammatory properties of leukocytes, macrophages, fifibroblasts, and endothelial cells, as well as of the secretion of cytokines/chemokines and growth factors [7].

In the early 20th century, Pneumonia was one of the dreaded diseases with mortality upto 40% even in treated cases. Before the advent of widespread use of antibiotics, Serum therapy was the only effective treatment for pneumonia, but it was expensive and carried a high risk of anaphylactic reactions. This led to the exploration of Radiotherapy as an alternative curative option for pneumonia in the 1930s. The hypothesis was that X-ray treatment would increase the metabolic digestion of the exudative material,leading to a resolution of the pneumonia.Calabrese and Dhawan [8] have compiled a review of all the reported studies on this topic from the United States. Between 1905-1946, fifteen studies showed that over 800 patients of bacterial, viral and atypical pneumonia were effectively treated by low dose kilovoltage X-rays. All these studies reported significant improvement in clinical symptoms within hours of initiation of therapy and decrease in mortality incidence to less than 10% in their patients which was comparable to serum therapy and sulphonamide treatment during the same time period. Irrespective of the age, health status, etiology and other diverse clinical settings, these researchers consistently reported the benefit of a single low dose X-ray exposure to effectively reverse the course of pneumonia. Benefits were uniformly better when radiotherapy was instituted in the initial stages of the disease. The target volume comprised of bilateral whole lungs and doses in the range of 20 to few hundred Roentgen were used, which given the attenuation through chest wall would likely have resulted in mean lung doses of less than 100 cGy range. The treatment became so popular that at one point of time some hospitals in US routinely treated pneumonia patients with therapeutic X-rays before admitting them for further treatment. However, with the emergence of the wonder drug Penicillin, the interest in this form of treatment for pneumonia gradually faded and there has not been a single published report in this aspect for over 70 years now.

The global pandemic of novel corona virus disease has once again challenged the medical knowledge and utility of existing therapies in preventing death from this form of community acquired pneumonia. In the absence of definitive treatment against SARS-CoV-2, clinicians have now turned to therapies with anecdotal evidence- the widespread use of Hydroxy-chloroquine for example. This scenario has once again aroused the interest of some radiation oncologists of the present era to revisit the century old hypothesis of low dose X-ray therapy in pneumonia as a potential treatment of COVID-19.

Possible mechanism of Radiation damage

Radiation can reduce inflammation by various mechanisms including induction of apoptosis by immune mediated cells, secretion of anti-inflammatory factors and reducing activity of macrophages [9]. The most accepted mechanism is via the 'Polarization of macrophages' to an anti-inflammatory or M2 phenotype. The M2 phenotype tends to suppress the over-action of the immune system whereas the M1 type over stimulates the immune system leading to Cytokine Storm [10].

Radiation as a therapeutic approach for Pneumonia

In a article published in Radiotherapy and Oncology journal in April, 2020, Kirkby and McKenzie [11] have called for a clinical trial to investigate the efficacy of whole lung low dose radiotherapy as potential treatment of COVID-19 pneumonia. They opine that a single fraction 30 to 100 cGy X-ray treatment could be easily delivered on a conventional megavoltage radiation therapy unit and at such low doses, common radiotherapy toxicities would not be of much concern. They believe it would present a very low risk to COVID-19 pneumonia patients, have the potential to reduce mortality and mitigate COVID-19 related burden on healthcare systems.

However, the astounding results of the studies of early twentieth century must be taken with a pinch of salt before we jump to conclusions. All the 15 reported studies by Calabrese et al [8] are case series of small number of patients, without randomization of subjects, no definite control groups for comparison or blinding of investigators, making their findings largely redundant in modern day practices of evidence based medicine. Only 2 out of the 15 studies quoted by Calabrese et al. dealt with viral pneumonia and SARS-CoV-2 being a positive-sense single-stranded RNA virus which still remains a mystery, whether the radiobiology of DNA damage applies for it, is also debatable. Add to that the complicated nature of planning and delivering bilateral whole lung radiation which comes with an inherent risk of cardiac toxicities and secondary malignancies. In today's era of precision and conformal radiotherapy, we are afraid, such an idea may find no supporters. Lastly, for a country like India where radiotherapy resources are already overburdened with existing cancer patients, incorporating COVID-19 patients into radiotherapy treatment facilities will be a herculean challenge.

In conclusion, although the idea of using radiotherapy as a potential cure for COVID-19 patients seems far-fetched, we believe its not entirely devoid of merit. The COVID-19 pandemic worldwide has cost millions of lives, totally destroying the healthcare facilities of most developed of nations. Hence all possibilities of intervention even with a glimpse of hope should be looked into. If ever there was a time to explore radiation as treatment for pneumonia on a clinically useful setting, we believe it is now.

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PERSPECTIVE

Cancer Researchers in Time of the Coronavirus Pandemic: A Time to Repurpose and Rethink

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Abstract

Since the outbreak of the COVID-19 pandemic the cancer researchers and patients around the world are looking at a uncertain future. The lockdown that followed the outbreak has derailed all the cancer research activities around the world. Labs have been shut and ongoing experiemts and drug trials have to be halted. It has resulted in to a catastrophic loss to patients and researchers. Since securing grants for research in todays competitive world is hard and there are deadlines to be met so many postdocs and principal investigators around the world are looking at a uncertain future. The pandemic has resulted in diversion of resources to contain COVID-19 pandemic which will lad to funding crunch in near future. In this review we try to address different issues faced by cancer research labs and discuss potential ways to survive this pandemic professionally.

Keywords: Cancer- COVID-19- research- funding

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Introduction

No reservations in saying that as a researcher life is tough. One devotes years asking novel scientific questions and performing experiments, and its years of resilience that pay with exciting results. And one fine day suddenly COVID-19 pandemic arrives and researchers cannot step back in to the lab, putting a halt to the work that would have might change the way in which we treat cancer. These are desperate times and thereby require desperate measures. There are no choices left at this point for a cancer researcher as one cannot step in to the lab to perform experiments on hard fought primary cell cultures derived from cancer patients which might not be the same when you revive them (after months of freezing). One cannot do anything about the murine model developed in the lab for osteosarcoma. This has actually been the scenario around the world since the outbreak of the COVID-19 pandemic, almost all the cancer researchers from trainees to post docs have to put a halt to their research activities.

We are living in an internet age so it will not be wrong to presume that modern society is well equipped to deal with disruption of workplace that comes with a pandemic. Many office workers engaged in IT and other related sectors already used to have flexible working hours and used to connect with colleagues around the world via internet-based apps from home. However scientists whose second home is a laboratory has been given a massive blow by this pandemic. Experiments have to be set aside for a indefinite amount of time, setting back many research projects around the world. Many labs are struggling to maintain basic upkeep of sensitive equipment and animal facilities, and facing hard decisions of what to let go. Technicians and other non-technical staff are worried that they will end up with pay cuts. Almost all research fraternity are unable to focus on the work and fear of getting sick by COVID-19 virus is getting worse with every day as the pandemic cases are reaching new heights with every passing day.

What's at stake

In our opinion it's the tax payer money that funds majority of research grants. The stalling of funding will have a bearing on many important research projects which run for a long period of time resulting in eventual deliverables. The disruption in continuity will result in failure to achieve the project goal leading to wastage of hard work and finance. In research, consumables are

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important commodities i.e. chemical, kits, plasticwares etc. Antibodies, kits, chemicals and culture ware (including flasks, media, serum etc) which are expensive and comes with shelf-life of 6 months to a year. So, by the time we are waiting for COVID-19 pandemic to end, we will lose a large sum of money on-shelves. Unfortunately, in south-east asian countries like India, COVID-19 arrived in-around March 2020. It's normally the time for the release of yearly instalments for on-going project grants, and as most of the government money has been shunted into the management of COVID-19 pandemic, researchers might get either reduced or delay in their next round of funding.

Money/time or both

Apart from money, the other important entity which researchers are losing is time. Research faculties, Postdocs, PhDs, Research Assistant, Technicians, if not associated with hospitals for COVID-19 are losing their precious time. Mid-level as well as final year PhDs, who have already planned their crucial or final experiments have to wait at least for 4-6 months, before they can actually start their work again. So, there is almost a delay of 9-12 months in their academic career (in best case scenario). Because of COVID-19 pandemic, we are observing delay in shipments of research consumables or delay in custom clearances. Quality science requires open borders which is not the case today as flow of reagents around the world has disrupted resulting in disruption of collaborative research also.

Cancer researchers staring at uncertain future

Things are very tough for both early carrier researchers like post docs who have just started their carrier in cancer research as they stare at reduced funding for cancer research in years to come, as the focus has shifted to COVID-19. Similar is the case with senior researchers who are at the brink of grabbing that tenure track position as they now compete for limited cancer grants which were already very competitive and hard to get. Altogether along with cancer researchers, cancer patients around the world stare at a very uncertain future. Funding crunch has already started to show up around the world. As an example Cancer Research UK (CRUK) announced that it will drastically scale back its research plans after the cancellation of a range of fundraising events and the closure of charity meant it will lose up to a quarter of its donated income over the next 12 months (which comes to about £120 m). Macmillan Cancer Support which is UK's second biggest cancer charity said that due to termination of fundraising events foundation is expecting the loss of up to half its fundraising income this year. which counts to about £100 m. This massive financial hit taken by two of the UK's biggest and best-supported charities is likely to put further pressure on ministers to launch a financial rescue package for charities which provide frontline health and social care services. The cancellation of "social fundraising" events in light of social distancing measures have resulted in cancellation of big fundraising events such as the London Marathon and closure of thousands of small and big charity events that has given cancer research a big halt in UK. CRUK has admitted that the reduced financial and research capacity could set back its fight against the disease for many years which would directly impact its goal to see three in four people survive their cancer by 2034.

Cancellation of Symposium /or Conferences

The overall cancer research has been harmed with prominent meetings in field of Cancer research being terminated or rescheduled. American Association for Cancer Research (AACR) made the decision to terminate the AACR Annual Meeting 2020, originally scheduled for April 24-29, 2020 in San Diego, California and finally decided to hold a virtual meeting American society for clinical oncology annual meeting, scheduled for May 29-June 2 2020 in Chicago. These cancer meetings serve as a mean to develop new collaboration and brain storming important trials in oncology which helps in advancement of Cancer treatment all together. The cancellation of these and other smaller meeting hurts the overall goal of cancer research. European Association of Cancer Research (EACR) is planning for virtual events for the rest of 2020 in order to bring researchers together.

Non-COVID-19 Researchers

During COVID-19 pandemic, the research labs have been shut down around the world, lab animals have been slayed, core research facilities closed as researchers have started working from home. So, how to best utilize your time if you as researcher/or research lab are not directly involved in COVID-19 management? For all the PhD students and Post Doc fellows our advice will be to utilize this time to brush-up concepts in area of your research. It's also a good time to look back in your research data and try to formulate the additional experiments for upcoming manuscripts and preparing for new experiments when you get back to the lab. For Research Faculties, in case they are still going to hospitals/laboratories can plan for their research proposals for next grant cycle. They can consider writing reviews within area of their expertise and try discussing the recently produced data with the collaborators. As per the EACR (European association for cancer research) blog, this is a great time for researchers to learn some new skills like honing up your dry lab skills like learning new bioinformatics tool and try to have as much virtual meeting with your lab group as possible and let it focus on other parts of life beside research. As researchers we don't get that much of the family time, I think this is a great time to devote with your children and make up for the times you lost when you were busy making world cancer free.

Research Labs at the forefront of fight against COVID-19

There is no denying the fact the fight against coronavirus cannot move ahead without understanding the mechanism through which virus infects humans, as it will help in developing drugs and vaccine against it to bring an end to the COVID-19 pandemic and saving millions of lives.

The research pace against COVID-19 has been something that has not been seen or documented in history of human kind. Situation of health institutions and regulatory bodies are better, if we compared todays situation with Spanish flu of 1918, when even antibiotics were not available. From discovering the sequence of the virus in identifying the mechanism of pathogenesis of the COVID-19 the pace has been prompt [1]. The PubMed search for COVID-19 yields 17,715 results, when last accessed on 1st June 2020 with majority of article appearing after Dec 2019 following outbreak of COVID-19) As of today, we have understood a lot about this virus [2], and that had made possible the development of medication against SARS CoV-2 in such a short duration of time [3], and several of them are still in pipeline at various stages of development. What is promising to see at these times is the way labs across the world are engaged in development of vaccine and drugs against coronavirus by sharing the data through open access platform, which is not normally thru [4].

In conclusion, the governments around the world should take critical decision in consultation not only with clinicians but with experienced virologists engaged in research and development of effective vaccine and therapeutics against coronaviruses. Governments can be better prepared for eventualities where a clinician who is engaged in the clinic with never ending patient load cannot understand. All the scientific and medical organisation of the country should work in tandem under one umbrella to ensure better research and clinical output instead of one organisation being given a lead and thus left with suboptimal results. Repurposing of cancer research lab in developing vaccines and better diagnostic methods against COVID-19 is the need of an hour, as all these labs have the equipment and manpower to do so.

Conflict of Interest

The authors declare no conflict of interest.

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PERSPECTIVE

The Impact of COVID-19 Pandemic on Oncofertility Services in Advanced Reproductive Centre UKM Medical Centre Malaysia

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Abstract

The COVID-19 infection is an infectious disease characterized by severe respiratory symptoms and was discovered as a terminal infection starting in December 2019 in Wuhan China. In Malaysia, our first Covid-19 positive cases found on 25 January 2020. Subsequently, there was an increasing trend of confirmed cases leading to the implementation of Movement Restriction Order (MCO) Act starting on 18 March 2020 aiming to flatten the infection curve. During this pandemic, UKM Medical Centre services were modified as hybrid-COVID-19 cluster hospital and treating both confirmed COVID-19 cases and standard cases. This modification is significantly affected overall our health management, including our oncofertility services. We were sharing the experience of the impact of Covid-19 toward our oncofertility services and modification to overcome it. We experience the reduction of oncofertility services uptake during this period due to both clinician and patient attitude while combating the pandemic Covid-19 battle in Malaysia.

Keywords: Oncofertility- COVID-19- Malaysia

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Introduction

The COVID-19 infection (Coronavirus disease 2019) is an infectious disease characterized by severe respiratory symptoms [1]. It was discovered as a terminal infection starting in December 2019 in Wuhan China and it had been spreading worldwide [2]. In Malaysia, our first Covid-19 positive cases discovered on 25 January 2020. Subsequently, there was an increasing trend of confirmed cases leading to the implementation of Movement Restriction Order (MCO) Act starting on 18 March 2020 aiming to flatten the infection curve. As of 28 May 2020; a total of 7629 confirmed cases with 6169 recoveries and a total of 115 deaths reported in Malaysia [3]. During this pandemic, UKM Medical Centre services were modified as hybrid-COVID-19 cluster hospital and treating both confirmed COVID-19 cases and standard cases. These modification is significantly affected overall our health management including our oncofertility services.

Newly diagnosed cancer with significant treatment-related gonadotoxic effect among children and reproductive age group will be referred for oncofertility review for Fertility Preservation (FP) treatment. The decision of the types of FP depends on allowable period before initiating the primary cancer treatment [4]. Choices of the embryo, oocytes, sperm and ovarian tissue cryopreservation are offered to tailor to the patient profile. However, due to the current global recommendation, the Assisted Reproductive Technique (ART) services are postponed due to COVID-19 pandemic [5]. Although the international body mainly European Society Medical Oncology (ESMO) and American Society Clinical Oncology (ASCO) has highlighted that FP is considered as an urgency among cancer cases and should not be deferred, majority of the oncology clinician are not aware thus less referral was made during this period [4-6].

In our oncofertility services, embryo cryopreservation is one of highest up-take; thus it required usual In Vitro-

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Fertilization (IVF) cycle including ovarian stimulation, oocytes pick up, intracytoplasmic sperm injection (ICSI) followed by standard cryopreservation. The additional cost of COVID-19 screening for both couple before the procedure added to the IVF cost and cancer treatment itself possess a significant financial burden to the couple. Furthermore, the stigma of visiting the hospital with fear of contracting the virus during treatment period leading to a higher number of couple decline the FP treatment in our centre. From our simple survey, most of our patient developed a complex emotional thought related to isolation or quarantine should they diagnosed with COVID-19, especially during receiving FP treatment. Therefore, they willingly opted out from FP treatment and barely followed the primary cancer treatment. Sadly we found that some of the cancer patients defaulted just due to this issue.

In cases for Ovarian Tissue Cryopreservation (OTC), we need to modify the laparoscopic procedure to a mini-laparotomy for oophorectomy. The laparoscopic route is currently prohibited in order to reduce the risk of aerosolizing of air droplet among the health worker. Thus, they required hospitalization as compared to the laparoscopic route. As most of OTC cases is prepubertal, we hardly receive any referral mostly due to anxiety of parent to accept the FP treatment and only concentrated with primary cancer treatment during this pandemic period.

In our oncofertility clinic setting was also affected as only two-person are allowed per clinic session. Previously, our clinic was conducted in the presence of a psychologist aiming to tackle the emotional element while proposing FP treatment effectively. The presence of family members as a support system is vital to ensure the synchronized decision is made with better FP outcome can be achieved. However, restriction of the number of people to reduce risk of COVID-19 infection leads to ineffective consultation, thus poor FP uptake. To overcome this, we activate the telemedicine via a phone call and video consultation as a platformed for FP consultation and information [7]. Despite that, the uptake is still low as this consider a new "norm" among patient and relative.

Although we do highlight that the oncofertility treatment should not be delay despite COVID-19, and modification of the services had been made, we foresee that the uptake will remain low. Therefore, we hope that physician dealing with cancer cases will be more proactive in referring suitable cases to oncofertility centre despite we battling with COVID-19 pandemic as it will significantly impact their life in future. We do provide a unique strategy in reducing the risk of infection during treatment and follow the standard operating procedure (SOP) as implement by the Ministry of Health. Therefore, the COVID-19 outbreak should not interfere with oncofertility treatment is aiming for a better future among cancer survivors. Otherwise, no financial or other potential conflicts of interest to declared.

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PERSPECTIVE

Low Dose Radiotherapy to Thorax for COVID-19 Patients: A Potential Weapon to Put the Dagger in Devil's Heart

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Abstract

The novel coronavirus SARS-Cov-2/COVID-19 pandemic has emerged as a major healthcare burden to the entire world. At the moment there is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection, mild upper respiratory tract illness to severe pneumonia with respiratory failure, multi organ failure and death. The inflammatory response induced in pneumonia is complex and involves a variety of mechanisms to defend against pathogens and repair tissue. During inflammation, activation of inflammatory cells releases cytokines and this intense inflammatory reaction can further to life threatening condition know acute respiratory distress syndrome. In the past, low dose radiotherapy has successfully cured patients with unresolved viral pneumonia. It was associated with reduction of mortality in unresolved pneumonias. Radiotherapy at low doses exerts anti-inflammatory effects which have potential to reduce the cytokine storm in COVID pneumonia patients. We hereby briefly touch upon COVID-19 infection and potential of low dose radiotherapy to reverse unresolved pneumonia, prevent development of acute respiratory distress syndrome as well as multi-organ failure.

Keywords: COVID-19- coronavirus- pneumonia- low dose radiotherapy

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Introduction

The last two decades have witnessed viral epidemics such as severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-03, H1N1 influenza in 2009, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [1]. Recently, novel coronavirus (SARS-Cov-2/COVID-19) has caused a viral pandemic, that has now become major healthcare concern to the entire world. This virus is highly contagious, human to human transmission occurs through respiratory droplets. The clinical spectrum of SARS-CoV-2 infection include a wide range of symptoms. This can be asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure, multi organ failure and death [1]. Recently sepsis has been identified as the most frequently observed complication, followed by respiratory failure, ARDS, heart failure, and septic shock [2].

The pathogenic mechanism that produces COVID-19 pneumonia are complex. In viral infection, viruses trigger immune cells to synthesize pro-inflammatory cytokines and chemokines inciting the immune response [3]. This intense inflammatory reaction as a whole is often referred a 'cytokine storm'. The effect is extensive tissue damage. The protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. It is also implicated into the pathogenesis of the cytokine release syndrome that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction [1].

At the moment there is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock [1].

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Radiation hormesis

Low dose radiation therapy (LDRT) has been successfully used to treat viral pneumonia [4-6]. The positive effects of radiotherapy have been attributed the phenomena known as radiation hormesis. Radiation hormesis is defined as a hypothesis where low doses of radiation (just above natural background levels) is beneficial, stimulates activation of repair mechanisms that protect against disease, that are not activated in absence of ionizing radiation [7]. The beneficial effect of LDRT were first described by Olivieri et al when they demonstrated that the adaptive response induced by low-dose radiation, induced cellular resistance to genotoxic effects caused by subsequently high-dose radiation (HDR) [8].

Properties of LDRT

Although, experimental studies pointing the exact underlying cellular and molecular mechanisms in this subset of disease are still rare and fragmentary, LDRT has clinically exerted anti-inflammatory effect on several benign disease and chronic degenerative disorders [9]. The modulation by LDRT on immunological response have been explored in vitro and in vivo [10]. These include leukocyte/endothelial cell adhesion, adhesion molecule and cytokine/chemokine expression, apoptosis induction, and mononuclear/polymorphonuclear cell metabolism and activity [10]. These mechanisms display comparable dose dependences and dose-effect relationships and are observed when radiation dose is < 1 Gy, maximum effect is seen in range of 0.3-0.7 Gy [10].

LDRT in Pneumonia

The inflammatory response induced in pneumonia is complex and involves a variety of mechanisms to defend against pathogens and repair tissue. During inflammation, numerous types of inflammatory cells are activated. Each releases cytokines and mediators to modify activities of other inflammatory cells [3]. This acute inflammation manifests as pneumonia or acute respiratory distress syndrome (ARDS). Because the lung is a vital organ for gas exchange, excessive inflammation can be life threatening.

In the pre-antibiotic era studies were conducted on animal models (guinea pigs, dogs cat and mouse) to assess the efficacy of LDRT for bacterial and viral pneumonias [4-11-12]. These studies supported the hypothesis that LDRT could reduce the effects of the pneumonia induced by bacteria or viruses and demonstrated that early initiation of LDRT was more efficacious in recovery of pneumonia [4].

In humans, LDRT successfully treated viral and bacterial pneumonia in the pre antibiotic era [4-6]. LDRT effectively cured pneumonia and relieved respiratory distress. Not only did it reverse pneumonia but also deceased mortality. There is significant reduction in mortality rate (30% vs 5-10%) in pneumonia patients with use of LDRT [4]. In a recently published review Calabrese et el reviewed 15 studies report that approximately 700 cases of bacterial, sulfanilamide non-responsive, interstitial, and atypical pneumonia were effectively treated by low doses radiotherapy. LDRT resulted in disease resolution, based on clinical symptoms, objective disease biomarkers, and mortality incidence. The study concluded that LDRT caused rapid reversal of clinical symptoms, facilitating disease resolution and that LDRT has capacity to suppress inflammatory responses which has widespread biomedical and therapeutic applications [4].

LDRT in COVID pneumonia patients

In the recent past LDRT has seldom been used to treat unresolved pneumonias and at the moment there is lack of robust evidence for suggest efficacy of LDRT against viral pneumonia. But, LDRT is effective and efficacious in treatment of viral pneumonia. Use of LDRT has resulted in significant reduction of morbidity and mortality for patients with viral pneumonias [4]. Never in the last century has mankind witnessed such a highly infectious viral pandemic with high mortality. Given the lack of any effective treatment and high mortality, LDRT seems a reasonable option to explore in moderately symptomatic (before the release of cytokine storm) COVID-19 patients with pneumonia. LDRT with its immune-modulatory properties has potential to resolve the pneumonia and reduce the cytokine storm which will prevent development of ARDS and reduce mortality.

Logistics in delivery of LDRT

There are ethical issues and logistics involved in to deliver radiotherapy in COVID-19 pneumonia patients. Treating symptomatic COVID-19 patients with pneumonias requires a dedicated radiotherapy facility as this poses risk of infection and contamination to the staff and radiation therapy unit. Disinfection of the radiation therapy machine and its room is possible but is technically demanding. Reducing risk of contamination during transport of COVID-19 patients from isolation to radiotherapy facility requires special prevention and disinfection protocols. There could also be apprehension regarding increased risk of second malignancy with use of LDRT among patients as well as the oncology and non-oncology fraternity. This is especially true if we assume that delivery of radiotherapy follows a linear no threshold (LNT) model. However, at low doses reduction of damage by adaptive protection equals to or outweighs radiogenic damage [13]. The LNT hypothesis for cancer risk appears to be scientifically unfounded and invalid in favor of a threshold or hormesis as observed within data from animal studies and human epidemiological observations on low-dose induced cancer [13]. Low doses radiotherapy is protective and is not associated with significant risk.

LDRT to the lungs appears to be a promising therapeutic option to be explored in this vicious viral pandemic that at the moment has no definite treatment. LDRT can rapidly reverse pneumonia and prevent cytokine storm (that leads to ARDS and multi-organ failure). Furthermore, it has potential to reduce burden on healthcare systems (oxygen dependence, need of intubation, reducing saturation of ICU & ventilator support).

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PERSPECTIVE

Socio-Cultural and Economic Impact of Corona Virus on Cancer Patients, Caregivers and Survivors

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Abstract

Corona Virus Disease -19 (COVID-19) pandemic has a widespread impact on social, cultural and economic aspects of life. It has affected cancer patients in a big way because with onset of COVID-19 pandemic, the healthcare resources were diverted to handle Corona virus infection. The cancer patient, their caregivers and healthcare professional are in dilemma of whether to continue the treatment or stop it for some time till COVID-19 infection settled down. The long-lasting effect of COVID-19 pandemic on socio-economic and mental health of cancer patients and health care workers will emerge in times to come. It is important that a tight balance be made between cancer treatment and its interruption due to COVID-19.

Keywords: COVID-19- Cancer care- mental health- BCG Vaccine- depression

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Introduction

World is facing a global health crisis unlike before. The novel COVID-19 pandemic has affected economic activities throughout globe including the health care industry. This has adversely affected people with chronic conditions such as cancer. Since Cancer treatment is time sensitive, immunocompromised patients appear to be at increased risk of COVID-19, and their outcomes are worse than individuals without cancer [1].

Elderly cancer patients having leukemia and other systemic co-morbidity are at a higher risk of ICU admission and even death. Patients on active cancer treatments such as chemotherapy, immunotherapy, radiotherapy, post bone marrow transplants and the survivors are vulnerable for COVID-19 infection.

Challenges in Delivering Care and Dilemma

As COVID-19 settles into the day to day reality across the globe, the question of how to keep at-risk patients safe from infection continues to be a challenge, particularly for cancer patients. While tele-consultations are increasing, but this virtual mode of communication has lot of limitation in terms of patient assessment and management. Also, tele-consultations are more of a use to follow up cases and not for newly diagnosed or patients under evaluation. There is a concern among patients of what happens if one stops, delays or switches the cancer treatment. Therefore, delaying or postponing cancer treatment due presumed increased risk of infection with COVID-19 is a matter of debate and dilemma.

According to the American Society of Clinical Oncology (ASCO), "There is no direct evidence to support changes in cancer regimen during the pandemic" [2]. Therefore, routinely stopping anticancer therapy is not recommended. But the fact is that oncosurgery, chemotherapy and radiotherapy is being rescheduled due to prevalent condition of Corona virus infection. It is also unclear that for how long the cancer treatment should be

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hold in a COVID-19 positive patient.

The paradox is exaggerated by the fact, that not treating cancer is even more dangerous as the diseases will continue to progress in the absence of treatment. The magnitude of collateral damage done to Cancer patients during COVID-19 pandemic is unimaginable.

The most unfortunate are the newly diagnosed early stage cancer patients where single modality of cancer care is curable, may become incurable. The chest symptoms (e.g. breathlessness, tachypnea) due to disease progression may be mistaken as COVID-19 infection and managed inappropriately.

Palliation is an ethical obligation even at the time of pandemic. Fewer patients are visiting palliative clinics due to lockdowns. Also, Community based palliative care of advanced cancers are affected significantly as health workers are following social distancing and there is increase demand of their services. Globally, due to increasing numbers of unexpected and premature deaths from COVID-19, the traditional and cultural rituals and ceremonies are prohibited in line with social distancing. Therefore, Families need extra support during bereavement.

Fear, Anxiety and Helplessness

Cancer diagnosis and its treatment-related anxiety and distress adversely affect the mental health of individuals and their families [3-4]. Because of better therapeutic options, the expectations of cancer patients have increased. But due to restrictions imposed in COVID-19 era, a point has come where patients and their caregivers, be it family members and/or health care workers are in a state of indecisiveness causing stress induced anxiety and depression. Their frustrations and anxiety related to constraints of treatment and limited follow up facility can be seen on social media. This has created a sense of loss of control over one's life and feeling of helplessness. On top of the emotional upset some patients are reported with psychosomatic symptoms such as diarrhea, muscle stiffness, headaches, and panic-related symptoms, e.g. sweating or increased heart rate.

The psychological stress in cancer patients during COVID-19 pandemic is due to lack of social security, difficulties in accessing oncology care, economic burden posed by the pandemic. Nothing could be worse than a cancer diagnosis at this time as delays in treatment is inevitable and delaying treatment seems like a double jeopardy. Thus the psychosocial needs of cancer patients and healthcare professionals should be assessed and taken care.

The health workers are no way spared. Many have been tested positive and lost their lives. The dilemma exists between protecting one's life and giving patients a good chance to fight their cancers during the COVID-19 outbreak.

Although tele-medicines are being used, physicians are not able to provide the best care to their patients. This is likely be the case for the next few months and there will be an inevitable impact on mortality and progression rates as the disease is time sensitive. This is also very emotionally challenging for doctors to absorb.

Socio-cultural and Economic Impact

Everything is super-strained in the whole world, be it is logistics of essential commodities to healthcare facilities [5]. Social distancing, wearing a mask, avoiding crowds and frequent hand washing are good preventive strategies against COVID-19 infection. But misinformation in society and prevailing misbelieves and myths led to isolation of cancer patients and survivors.

Cancer care in developing world is challenging. Because of limited numbers of skilled healthcare professionals and resources in terms of infrastructure, the quality of care is also suboptimal. This has been amplified by the COVID-19 ill effects on healthcare of cancer patients which require urgent measures. The vulnerability of cancer patients can be measured in terms of availability of healthcare services, economic burden and psychological issues arising due to strict lockdowns.

Cancer treatment will change enormously in comings days. It is predicted that the cancer mortality and morbidity will increase, not because of the corona virus pandemic, but because cancer patients would not be treated as they should be normally. The unintentional delays in surgeries and other cancer treatments would result in poor outcomes. Moreover, with shrinking opportunities of earning, loss of job, and travel restrictions, a good proportion of patients will default on their treatment.

Triaging of patients based on risk stratification of cancer therapy and routine follow-up visits during these difficult times, in an attempt to protect vulnerable patients and staff [6]. With the current limitation of goods transfer, there is a possibility of shortage of drugs essential for cancer treatment. The possibility of further delay in treatment and uncertainties could affect the mental health and quality of life of both patient and oncologists.

Free meals and financial support to poor and needy is being provided by the government of India. Financial security in form of insurance for the frontline health workers has been also introduced. Hopefully this will strengthen their courage to fight against cancer and corona both.

Moreover, the ban on social gatherings including religious activities is scientifically justified for containment of COVID-19 infection but is likely to exacerbate the issues related mental health [7].

Few researchers have proposed that India may have some protective immunity against COVID-19 infection. The different factors in relation to COVID-19 infection, its virulence and patient outcome need to be ascertained with evidence. These include high temperature and humidity, age, widespread BCG vaccination and resistance to malaria. Also, whether these factors have a role to limit the severity of COVID-19 infection in Indian context needs to established with robust data.

Due to lack of clinical evidences, BCG vaccination is not recommended by World Health Organization (WHO) for the prevention of COVID-19 [8]. However, WHO continues to recommend neonatal BCG vaccination in countries or settings with a high incidence of tuberculosis

[9]. Therefore, further clinical trials are required to establish a true link between COVID-19 and BCG or malaria burdens.

In conclusion, no one knows what choices to make for cancer patients and what is the right suggestion to be advocated in view of fear of cancer recurrence, progression to a higher stage and loss of life due to inability to access the system amid COVID-19 pandemic. It is scary for oncologists, and of course, for many cancer patients, survivors and the caregivers.

Multidisciplinary approach using innovative ways to collect empirical data of cancer patients and available health care facilities is the need of the time. This will help to formulate policies for cancer care in the face of the pandemic.

With the positive collaborative efforts, we can win this war against the pandemic. We know this pandemic will be tackled over a period of time, but it will leave an unforgettable impact on cancer patients and their caregivers along with oncologists who are helpless on deciding whether "to treat or not to treat."

Oncologists have to think out of box to deal with cancer patients during the time of health emergencies. A special emphasis is warranted for cancers in elderly patients as they are more prone for adverse outcomes both because of disease and COVID-19.

Apart from educating our cancer patients, we must try to practice hygiene along with social distancing, as infection to one healthcare professional will force all contacts to go into quarantine affecting the whole system very badly.

Patients should be advised to take consultations via electronic mediums rather than physical visits. Healthcare professionals need good communication skills to counsel and advice the patients through tele-medicine.

To summarize, interdisciplinary resource team should be to created policy for combating COVID-19 infection during cancer care, strategize to reduce personal visits and empowering patients and caregivers through use of communication using digital technology. In addition, palliative and supportive care services for people with advanced cancer during the COVID-19 outbreak should be made available through various platforms i.e. tele-consultation, engaging nongovernmental organizations (NGO), and volunteers.

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PERSPECTIVE

Tobacco Smoking and Risk of Novel Coronavirus Infection

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Abstract

Tobacco consumption, specially smoking and waterpipe, affect the lung capacity which may lead to difficulty in breathing, caused by long term harmful effect on cardiovascular and respiratory system leading to elevated risk of various kind of infectious diseases. SARS-CoV-2 infection, which primarily affects the lungs, is found to be associated with severe events in persons who consume tobacco either smokeless or with smoke. Many studies showed that smokers, either current or former, show the severe COVID-19 progression. Yet there is no strong evidence which establishes the link between tobacco smoking and COVID-19. Smoking causes increase in secretory cells of respiratory tract, subsequently increasing ACE-2 expression. Ageing is also associated with a higher expression of ACE-2 gene. This can possibly explain the vulnerability of aged people, smokers and patients with hypertension to coronavirus and also people who consume tobacco, either smokeless or smoke, as a potential vulnerable group for COVID-19.

Keywords: Tobacco- smoking- COVID-19- SARS-CoV-2- Coronavirus infection

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Introduction

Coronavirus disease 2019 (COVID-19), caused by a type of coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has emerged as a public health crisis. Till mid-June 2020, the most affected countries like USA, Brazil, Russia, India, UK, Spain and Italy have reported more the 50% of 7.5 million COVID-19 cases. The overall mortality due to COVID-19 is reported close to half of million people, making it the biggest public health crisis of current era [1]. Initially thought to be primarily a disease affecting lung and causing pneumonia, now found to be involving various tissues and systems including causing thromboembolism, stroke and renal failure.

Though, coronavirus infection is affecting all age groups, sex, race, ethnicity and continents, few groups or people are more susceptible to getting infected with coronavirus and few of them have higher chance of adverse disease progression including death. The risk factors for COVID-19 are old age people having co-morbidities including diabetes, hypertension, cancer, respiratory diseases, cardio-cerebrovascular diseases and renal diseases. Patients with these co-morbidities are found to be at a higher risk of severe COVID-19 progression including deaths [2].

Tobacco smoking is a known major risk factor associated with many of these disease conditions, especially related with respiratory system [3]. Tobacco consumption, specially smoking and waterpipe, affect the lung capacity which may lead to difficulty in breathing added by long term harmful effect of cardiovascular and respiratory system leading to elevated risk of various kind of infectious diseases [4]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, which primarily affects the lungs, is found to be associated with severe events in people who consume tobacco either smokeless or smoke. Yet there is no strong evidence

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which establishes the link between tobacco smoking and COVID-19.

Tobacco is being consumed worldwide in various forms which include tobacco chewing, paan masala, bidi, taibur (liquid water), cigarette smoking etc. Thus, people who consume tobacco are also found to be at an increased risk of contracting SARS-CoV-2 infection. The reason behind smoking being a risk factor for COVID-19 can be linked with Angiotensin-converting enzyme II (ACE-2). Expression of ACE-2 gene is increased in people who smoke. ACE-2 is found to be associated with SARS-CoV-2, which uses it as a receptor for cellular entry. Smoking causes an increase in secretory cells of respiratory tract, subsequently increasing ACE-2 expression [5]. Ageing is also associated with a higher expression of ACE-2 gene [4]. This can possibly explain the vulnerability of aged people, smokers and patients with hypertension to coronavirus and person who consume tobacco, either smokeless or smoke, as a potential vulnerable group for COVID-19.

Tobacco smoking makes respiratory system prone to many infections. Consumption of tobacco, either smoke or smokeless, is responsible for destroying the cells of immune system as reported in many studies showing that smokers are more prone to the allergic symptoms (influenza like) and higher deaths recorded in previous Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreak among smokers in comparison to non-smokers [4]. Smoking and consuming smokeless tobacco products can possibly correlate with the severities of COVID-19 morbidities, as many evidence based studies highlighted the negative impact of these products on lungs health including COPD (Chronic obstructive Pulmonary Disease), severe degree of pneumonia and cancer, on heart including coronary heart disease, stroke and hypertension [3-6].

Higher rate of severe events are found in people who are infected with coronavirus, and having co-morbidities like hypertension, cancer, diabetes, respiratory problems [2]. Tobacco smoking is associated with higher rate of severe events in Coronavirus disease (COVID-19). In US, around 7162 cases of COVID-19 with complete history of health related data found that 3.6% of cases were current or former smokers and contributes to 6% and 8% cases of hospitalized and Intensive Care Units (ICUs) admission, respectively [7]. Many of the studies conducted in China also reported higher ICU admission rate of patients having history of smoking, either current or former [4].

According to Chinese research study, smokers, either current or former, show the severe COVID-19 progression. In all patients with severe disease progression, every 1 out of 5 was a smoker, 16.9% current and 5.2% former smokers, while only 11.8% current and 1.3% former smokers were found with non-severe COVID-19 symptoms [8]. Many observational studies found that percentage of smokers is 1.4 – 18.5% of hospitalized cases of COVID-19 and severity of COVID-19 is higher among them with an odds ratio of 2.2 [9].

Another research study of china shows that the progression (symptom severity) group had a significantly higher proportion of patients with a history of smoking than the improvement/stabilization group (27.3% vs. 3.0%, χ^2=9.291, P =0.018). The progression group was found to receive higher respiratory support in comparison to the other group [10].

Smoking is the biggest cause of lung cancer in developed and developing countries. Patients with lung cancer were found at a higher risk of coronavirus transmission among all cancer types with an increased risk of severe events and deaths. Among all the deaths in patients with cancer due to COVID-19, deaths in patient with lung cancer contribute highest [4].

The world is already facing burden of tobacco related diseases and COVID-19 may be the new entry in this. Though there are limited studies available which show the severity of COVID-19 progression and outcome in people with tobacco consumption, and more robust data is needed to establish the relation, but in view of the current pandemic, evidence suggests implementing tobacco control and smoking cessation strategies more strictly to reduce further burden.

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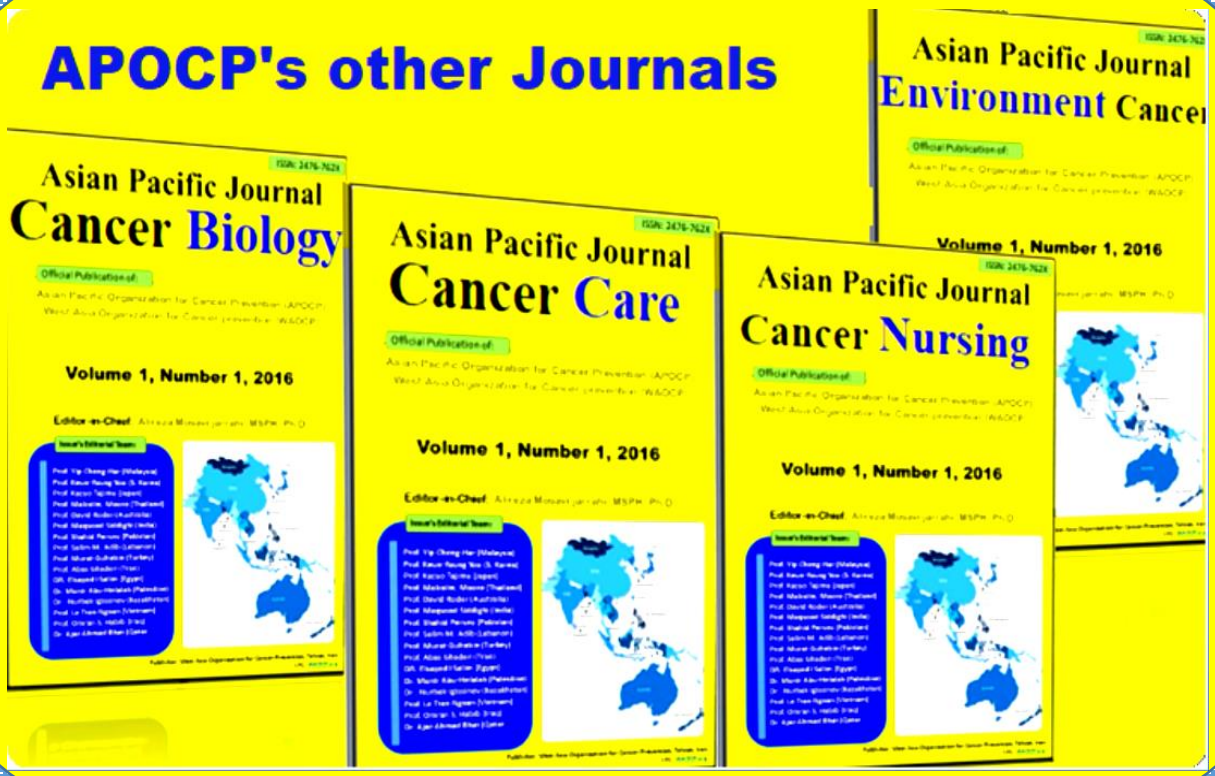

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