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Impact of the COVID-19 Pandemic on the Cancer Care Ecosystem – Review and the Road Ahead

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Background

The novel Corona virus pandemic has significantly altered the dynamics of clinical practice. As one of the most contagious respiratory infections known to mankind spreads across the world, with no established curative medication or preventive vaccination, at the time of scripting this article, most healthcare institutions have been forced to incorporate restructured clinical operations and practice protocols. Prioritization and maximal diversion of resources towards the management and care of COVID-19 patients has become the new norm, as the global disease load spike is steeper than all previously documented pandemics [1]. Origin of the novel coronavirus, a member of the SARS family retrovirus, was first reported in the Chinese city of Wuhan in late 2019, although the theories of origin between a purely zoonotic jump from bats to humans or possibility of a laboratory misadventure from the Wuhan Institute of Virology remain unproven till date.

Medical systems across the globe continue to face challenging insufficiencies to meet demands of a pandemic of this magnitude. Two globally acceptable modules for countering the magnitude of this outbreak are 'social distancing' and 'diversion of all possible medical resources for the management and care of COVID-19 patients', both in combination with widespread COVID-19 testing. The resultant multi-dimensional scarcity of resources and services for cancer patients across medical systems are reviewed in this article. With all non-emergency modalities of healthcare being either diverted or withheld for currently uncertain periods, cancer management protocols need to be revisited and redefined, as deferred diagnosis and delayed treatments will lead to increase in burden of advanced cancer cases. Scarcity and redistribution of resources also have the potential to exacerbate morbidity and mortality scores across various cancers. The challenges oncologists will face during post-first wave of the pandemic need to be anticipated. Presence of cancer patients in crowded hospitals and also potential exposure to the oncology clinical teams need to be evaluated and strategies whereupon cancers can be monitored through incorporation of liquid biopsies thereby averting interventional practices, and, therapy decisions made on the basis of personalized precision diagnostics must be considered [2].

Overview of Corona Virus

The pathogenic entity causing COVID-19 also known as novel Corona virus pneumonia (NCP) is from the β-sub group of SARS family Corona virus. The International Committee on Taxonomy of Viruses (ICTV) has named this virus SARS-CoV2 [3]. The viral pandemic is the result of the significantly higher transmissibility of SARS-CoV2 wherein one infected individual further infects 2.2 to 3.6 healthy contacts, which is higher than the earlier MERS and Ebola outbreak (figure 1), despite the lower mortality rate of the former[4]. The single stranded RNA of SARS-CoV2 reveals 96% resemblance to bat SARS coronavirus (SARSr-CoV-RaTG13, MG772933) indicating a possible origin from its nonpathogenic predecessors - bats via a possible intermediate host – the pangolin[3]. The prospect of a human pandemic could possibly have been predicted much earlier, as the SARS CoV2 is the 7th member of the coronavirus family that has infected humans following earlier attacks by SARS-CoV and MERS-CoV [5]. However, healthcare systems across the globe continue to showcase a grim picture and lack of preparedness towards control and containment of such a predictable pandemic.

The receptor binding domain in 'spike' protein of SARS-CoV2 attaches to ACE 2 receptor of respiratory epithelial cells in human hosts [6]. Structural models have deciphered that the SARS-CoV 2 exhibits ten-fold higher affinity to the ACE 2 receptor than the predecessor SARS coronaviruses indicating its higher infection rate [7]. The other peculiars feature

of SARS-CoV2 is that it has a relatively prolonged incubation period of 0 to 24 days but replicates aggressively in its host even during the asymptomatic incubation period resulting in potential transmission to humans who come in direct contact during this period [8, 9]. Although the predominant mode of transmission documented so far is via aerosols emitted from nose and mouth of the infected individuals, viable viral presence has been detected in stool, urine, tear and saliva as well. High viral load of SARS-CoV2 has been detected in gastrointestinal tissue samples indicating that the digestive tract might be a potential route of infection [10, 11]. Feto-maternal transmission has not yet been proven to occur in late pregnancy although data is limited [12].

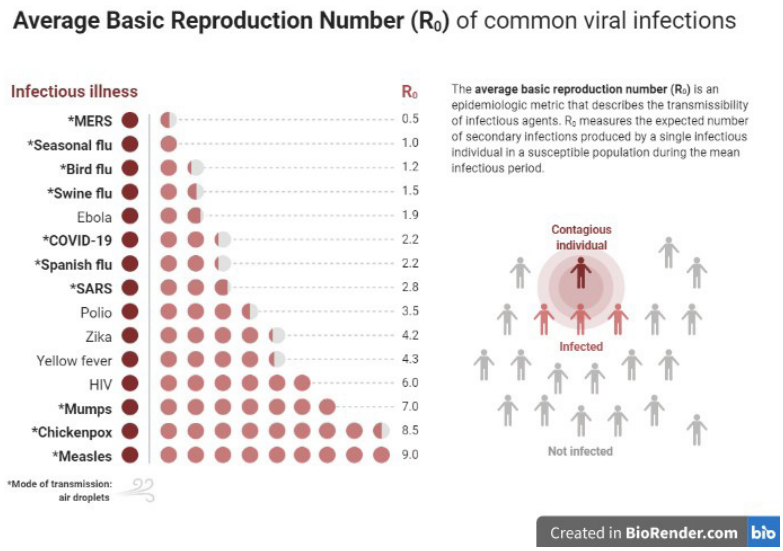

Figure 1: The average basic reproduction number (R0) representation

Demographics of COVID-19 emerging from different countries clearly indicate that although a disease of relatively lower mortality than its predecessors like the SARS and MERS, COVID-19 will result in much higher deaths worldwide due to its higher virulence and transmission rates[13], alongside its peculiar predilection to cause more deaths in older patients (> 60 years of age). Currently practiced social distancing and mass lock downs across continents target to break the direct human transmission of this highly contagious virus however modes to curtail surface to human transmission are weaker as this virus is known to survive for extended period of time on inanimate services like plastic, cardboard, metallic surfaces etc [14, 15].

Immunopathology of SARS-CoV2 in Humans

80% percent of COVID-19 positive cases tested worldwide till date have initially presented as asymptomatic individuals (figure 02). Only 15% patients present symptomatically while 5% may require critical care intervention and ventilatory support. Common findings in hospitalised patients include lymphopenia, neutrophilia, thrombocytopenia, elevated IL-6, raised CRP and pneumonia with characteristic pulmonary ground glass opacity on chest CT [16-18]. Another common finding in fatal and clinically severe cases is a surge in pro-inflammatory cytokines like IL2 , IL 7 , IL 10, GCSF , IP10 , MCP-1 , MIP-1A and TNF-Alpha [17] indicating that “cytokine storm” may have a major role in the pathogenesis of COVID-19 [19-21]. Such cytokine storm leads to life threatening complications in fatal cases leading to exacerbated pneumonitis, ARDS, respiratory failure, cardiogenic shock and renal failure [13].

Correlation of Pro-inflammatory Cytokines to Cancers

Cancer cells express antigens that can be recognised by both the innate and adaptive immune systems. Host derived cytokines can suppress tumour formation by instigating a tumour specific inflammatory immune response. While on the other hand, tumour cells can also exploit host derived cytokines to promote growth, increase resistance to apoptosis and foster dissemination. The impact of COVID-19 mediated immunogenic flare and its effect on existing cancers is yet to be evaluated [13]. Mortality is significantly higher in COVID-19 affected cancer patients [22].

Patients with cancer are known to be at an increased risk for community acquired respiratory viruses, such as influenza, due to their frequently observed immunocompromised state [23]. The spread of SARS-CoV2 is of particular concern in this vulnerable population, given the higher case fatality rate seen in Wuhan, and the increased severity of the course of disease with COVID-19 [23,24,25]. In smaller cohorts of cancer patients evaluated at Wuhan, mortality was found to be double, (5.6%) of that observed in patients of, COVID-19 without cancers (2.1%) in the same age group [26].

Another recent study from a hospital system in New York observed 28% mortality amongst cancer patients affected with COVID-19 although there was no correlation between ongoing active chemotherapy and radiation therapy in this study [33].

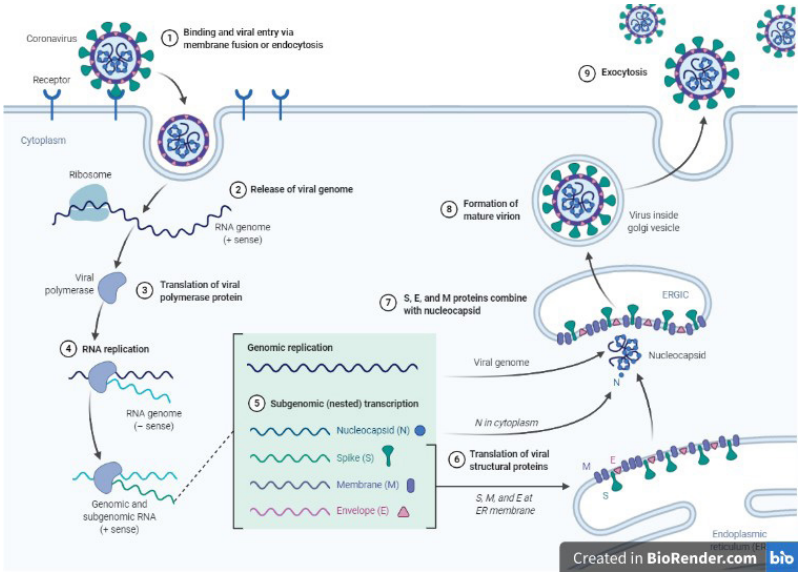

Figure 2: Coronavirus pathogenesis

Mortality of COVID-19 is significantly higher in older adults [33]. Since most cancers have median age of presentation shifted towards >50 years, it would be worthwhile to evaluate if co-prevalence of cancers and COVID-19 will impact median survival of humans till curative treatments or vaccines are available. A host of antiretroviral therapies currently under trials need to be evaluated for their impact on pre-existing cancers, interaction with anti-cancer drugs and also possibly towards cancer-enhancing activity as well. From a therapeutic standpoint, immunomodulatory drugs primarily impacting immune checkpoints might have shift in response in presence of a plethora of immunostimulatory pathway activation by the SARS-CoV2 virus, this needs further investigation.

Mathematical epidemiologic progression models from the Department of Immunology and Infectious diseases at Harvard have projected that infection by the SARS-CoV2 is likely to follow trends of seasonal spike and trough [27] similar to the disease trends of other beta coronaviruses like OC43 and HK1, and hence will necessitate intermittent social distancing practices till as long as 2024[28]. The study further proves through statistical models that the currently enforced 'one time social distancing efforts' may push the SARS-CoV2 epidemic peak into the autumn season, potentially exacerbating the load on critical care resources if there is winter time transmissibility. Hence, intermittent social distancing might maintain critical care demand within thresholds. With such a long term impact on medical practice norms, the follow up protocols for cancer patients who have completed chemotherapy needs to be surely re-evaluated.

With treating oncologists as drivers and telemedicine tools as enablers, modules of remote-assessment of tumor burden will have to be incorporated into practice. One of such cancer assessment module could be through liquid biopsies which co-assess circulating tumor DNA and circulating tumor cells at high sensitivity levels and hence alleviate need of contact practices like tissue biopsy and PET-CT scans.

Current Cancer Scenario and Impact on Global Healthcare Systems

In the mid of April 2020 the EMA (European Medicines Agency) announced that cancer related deaths in Europe are declining, which is a great success, but it remains unclear how COVID-19 will impact this. Most screening programs for preventable cancers (gynaecological and colorectal cancers) are likely to get postponed till the pandemic spike slopes down. As the end of COVID-19 is unclear, whether a surge in cancer cases is witnessed due to the delayed screening and preventive check-ups will be clear in the coming months. German insurances noted 20% less hospitalisation of cardiac patients since the outbreak of COVID-19. While the cause remains unclear, they speculate that it might be apprehension towards acquiring the virus iatrogenically. However, there is likely to be a spurt in cancer patient numbers, after the crisis abates.

Obviously the situation differs across different geographies worldwide concerning the impact on the healthcare system, while the Intensive Care Units (ICUs) in southern Europe/US are overwhelmed, other countries are still able to manage and do not see a negative impact. The reasons behind this variance remain speculative, and cancer patients across different

healthcare systems that are struck by COVID-19 are likely to get optimal treatment compared to before COVID-19. Another challenge due to the hampered supply chains are ongoing clinical trials, as the healthcare systems in some countries remains overwhelmed by COVID-19. With prolonged duration of the global shutdown, important scientific outcomes might get hindered or diluted.

Currently as the economies worldwide hold their breath, the larger question is how long will it be able manage without inflicting irreparable damage in the coming months or years? The pharma and medical device industry have become more and more global over the past decades. However, the current crisis has shown vulnerability in the global supply chain, with reference to logistics of generic drugs, safety equipment and diagnostic consumables. It is not unlikely that the manufacturers of chemicals for pharma and medical products will partly shift away from existing overseas locations with support of the local governments. It is likely that we see a less globalized world after COVID-19. Medical tourism has already been severely impacted, and cancer care, being a key component therein, has taken a severe hit.

The EMA has issued recommendations on how to avoid supply bottlenecks during the Coronavirus crisis, as the current pandemic has significantly increased the demand for certain drugs. 30% of infected people need to be treated in hospitals; those who need intubation in addition to oxygen also need anaesthetics, antibiotics, muscle relaxants, antidiuretics and resuscitation drugs. For these groups, the need has increased significantly. Most of the anticancer drugs depend upon the type and stage of disease. Healthcare systems need to ensure that they do not witness a breakdown in the supply for those medications as patients will certainly suffer as an outcome of the same. Therefore, it could be worthwhile to consider, wherever possible, that cancer patients receive personalised therapies identified for them using advanced diagnostics, ranging from molecular profiling of tumours to pharmaco-genetic studies and evaluation of predictive biomarkers so as to define the most effective line of treatment.

Shutdown of international borders has stopped medical tourism, and as the healthcare ecosystems look for future investments, adoption of state of the art and evidence based innovations within individual countries would positively impact the ability to attract investments. Post COVID-19, health related travel is likely to become less frequent, especially if the respective countries react fast enough, to strengthen their cancer delivery services.

Possible Solutions and New Technologies

It is clear that the worldwide healthcare systems need to stay or become agile, because nobody can predict for sure where the crisis will finally lead. It depends if we see in the coming months a second wave of COVID-19 or mutations of the virus, which would further adversely impact cancer patients. From the current situation, it is obvious that new technologies including genetic testing need to be ramped up. It is essential this is undertaken in a sequential manner that does not erode any quality metrics, to prevent false negative or false positive results to truly identify what we are facing. Several instances of low quality tests already have impaired the faith in healthcare systems. Countermeasures for such situations need to be in place in future. For cancer patients it becomes more important in such times, that they achieve high success in their chemotherapy treatments.

Although certain studies have recommended prioritization for specific type of cancers and treatments thereof [34], the application of such discrimination in cancer care, in practice, may lead to delays in cancer screening and lapses in aggressive treatment, thereby potentiating a flare up of cancer burden in near future. It would be valuable to explore alternate solutions where patients do not have to undergo complicated and resource intensive testing, but can avail new technologies relying on simple blood draws to diagnose cancer when suspected. This would lead to a diminished pressure on healthcare resources needed elsewhere. Holistic molecular profile based personalised treatment selection on the other hand might reduce the burden on conventional chemotherapy and radiotherapy units.

To reduce the risk of infection to patients and staff members, several cancer institutions, including The University of Texas MD Anderson Cancer Center in Houston, Memorial Sloan Kettering Cancer Center in New York, and Dana-Farber Cancer Institute in Boston, have cancelled all international and domestic work-related travel for meetings or conferences. We have to find new ways to communicate and exchange scientific information efficiently. Conferences will have to be reconsidered, for example the AACR is being held virtually online.

With the already skewed ratio of oncologists in Indian subcontinent wherein only 1 oncologist is available for over 2000 cancer patients (IIHMR Study 2017), even a minimal loss of oncologists' work hours due to disease morbidity would be devastatingly detrimental to the cancer management cycle. Hence, strong consideration must be given to safeguarding the health of medical staff treating cancer patients. This would require stringent planning especially for activities such as 'screening and diagnostic' visits as well as post treatment 'follow ups'. Modalities of remote monitoring of cancer status

need to be incorporated into standard management practices.

While recommendations from most oncology societies like ASCO, ESMO, ESSO and the Global Radiation Oncology Targeted Response which emerged from an online discussion involving 121 contributors in March, 2020 have all recommended stratification of 'low priority' cases and to defer management for this category. The prevailing clinical practice situation might be different, especially across the private payment healthcare systems. Clinicians need to prepare for a plan B for monitoring patients through modalities of liquid biopsies and also consider more evidence-based personalised therapies which might recommend oral medications that can be self-administered by the patient [29].

ASCO recommendations for oncologists at the time of pandemic categorically mentions that decisions pertaining to allocation of scarce resources should not be made by oncologists and should rather be left to management committees; however the oncologists should support informed allocation decisions by providing accurate, up-to-date information about cancer-related prognosis and oncology treatment options that are relevant [30]. This establishes the use of the latest technologies in liquid biopsy and therapy recommendations based on modalities of precision-oncology for prognostication and making management decisions during such times.

There is little doubt that telemedicine providers globally will see a huge uptick in demand for their services. This demand is unlikely to wean away till we are well past the pandemic or until widespread vaccination is made available at the least. However, it is not unlikely that habits often grow into default preferences and telemedicine solutions continue to gain strength as a major force in the healthcare ecosystem. The Ministry of Health, Government of India has issued specific 'Telemedicine Recommendations' for doctors and healthcare establishments which mentions of counselling in context to initial assessment, follow up evaluation and counselling for anticancer drugs. All such complex evaluations and consultations can be immensely leveraged through supportive modes that enhance such assessments and also possibly aid towards disease quantification [31]. Assessment of molecular landscape of tumors and detection of vital tumor information via liquid (blood based) biopsies may tangibly reduce need of travel at such crucial times of social distancing. The guideline specifically upholds value of telepathology and tele-radiology services in supporting patient care during the current pandemic [31].

Role of Comprehensive Molecular Testing

Molecular science offers enormous potential in transforming the current strategies undertaken to prevent, diagnose and treat cancer. With the benefits of comprehensive molecular testing including genomics getting increasingly established, efforts must be made to increase access to these services for all who can benefit. The focus for this solutions should not remain confined to the identification of `targeted therapy' for specific cancers, but should be used more holistically to serve cancer patient in given circumstances of restricted access. Newer evidences and data points, along with screening tools, are now available with healthcare professionals that identify individuals who can benefit from such tests. Greater access to credible and reliable information, along with consumer involvement in healthcare decision-making, is accelerating the pace of this change. Personalized oncology is aiding better understanding of genetic change in tumours, and new customised therapeutic interventions are being used to target the genetically different sub types of cancers. It is crucial not to forget the intra-individual differences of cancer cells in a single patient and to use intelligent algorithms interpreting the results to determine the best working combination therapy rather than to rely on single treatments, especially in late stage patients.

With current restrictions in accessing non-emergency cancer care or apprehensions in visiting healthcare facilities due to fear of the highly contagious COVID-19 infection, new avenues of innovative technology will continue to gain momentum to support the patient as well as clinical needs. As previously mentioned, due to the overwhelming of healthcare facilities and prioritisation of resources towards battling the pandemic, cancer patients are already beginning to struggle for continuum of ongoing treatments & proposed elective procedures for diagnosis and monitoring of disease burden. Innovative biotech solutions will continue to offer increasing opportunities of managing these deficiencies, with the use of blood-based genomics. These solutions come with convenience of simple blood draws from the patient's home, and can enable cancer care systems to stratify and prioritise their patient's basis their existing and depleted resources. Adoption of blood-based solutions to help identify cancers and provide initial treatment as well as recurrence monitoring is becoming common by the day.

Physical biopsies are often required in case of inconclusive pathological findings or absence of adequate tumour tissue for analysis. Such procedures are resource intensive and add to existing burden of the healthcare system. Non-invasive methods which can reduce the dependence on invasive biopsies, and offer attractive substitutive options. Detection of blood-based circulating cancer analytes in cancer patients like circulating DNA and tumour cells may indicate the

biological activity of malignancy, irrespective of clinical or radiological status [32].

While it is well recognised that there is room for much improvement in positioning the latest biotechnology modules within management pathways of cancer patients; therapeutic algorithms in cancer management need to be redesigned after judicious cost benefit analysis in context of implementing more effective yet affordable management strategies with the combination of biomarkers and genomics. Patients and caregivers need to be informed about the latest scientific advances, which can help oncologists administer therapies that are more effective and financially beneficial, thus achieving the common goal of affordable and successful cancer care.

The cancer burden continues to increase, and we will need to find alterations in operating models, which focus on better and sustained health outcomes, not just cost containment. The proportion of patients receiving advanced tests will only increase as more data points enumerate the benefits of such solutions. Increasingly, data capture related to clinical treatment, molecular and imaging records need to be constantly gathered and combined with predictive analytics to deliver best care. However, additional factors like regular cancer screening, adoption of healthy lifestyle, vaccination, and avoiding tobacco and alcohol consumption remain critical factors in not just preventing cancer, but also enhancing early stage detection and in achieving better management outcomes.

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