

CANCER CARE IN COVID-19 CRISIS: PANDEMIC OF THE 21ST CENTURY

Oncology

Poojar Sridhar	Assistant professor Department of Radiation Oncology Kidwai Memorial Institute of Oncology Bangalore-29
Vijay Calmuge Raghu	Associate professor Department of Epidemiology and Biostatistics Kidwai Memorial Institute of Oncology Bangalore-29
Mahantesh A S	Assistant Surgeon Kidwai Memorial Institute of Oncology Bangalore-29
Kalyani B*	Post Graduate Student Department of Radiation Oncology Kidwai Memorial Institute of Oncology Bangalore-29*Corresponding Author
RaslaParween	Department of Radiation Oncology Kidwai Memorial Institute of Oncology Bangalore-29
Arunkumar A. R	Associate professor Department of Pediatric Oncology Kidwai Memorial Institute of Oncology Bangalore-29

ABSTRACT

Background of Study: A newly emerged human coronavirus (COVID-19) was reported in December 2019 in Wuhan, China. COVID-19 is transmitted through droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic carriers. Cancer care is challenging in the current COVID-19 crisis. At present, about 13 lakhs new cancer cases are reported in India. In Karnataka, about 78000 cancer cases are reported every year. Many studies have already reported smoking as the main risk factor for lung cancer. The ACE receptors are seen in very high level in smokers, which is also the nidus for the corona viral infection. **Materials and Methodology:** Kidwai Memorial Institute of Oncology (KMIO) has a Hospital Based Cancer Registry (HBCR) and more than one fourth cancer cases of Population Based Cancer Registry (PBCR) is from the base Institution. COVID-19 Incidence, Guidelines for management of COVID-19 is obtained from Ministry of Health and Family Welfare, Government of India. Join point regression analysis was used to calculate the cancer trend and tabulation and graphs are used for descriptive analysis of COVID-19 cases in Karnataka and India. **Results:** There is an exponential rise in COVID-19 positive cases. With this increasing trend all over the country, the number of cancer patients getting infected is also high because of immunocompromised state. After 2000, it observed 2.1 percent annual change in males and 2.2 percent annual change in females. Average annual percentage change (increasing cancer) for male cancers is 0.9% and 0.8% for females, a significant increasing trend for both the gender is observed in Bengaluru PBCR. **Conclusion:** In the present Health emergency of COVID-19 crisis, Cancer care is being affected by this pandemic disease. Increasing trend is seen in Cancer incidence in India and also in Karnataka. There is exponential increase of COVID-19 positive cases in India and Karnataka. Delay or long postponement in Cancer treatment will result in compromising local control rate and overall survival. COVID-19 screening and testing must be done compulsorily before starting cancer treatment. Shorter treatment regimens with minimal human resource wherever possible must be considered. Chemoprophylaxis with hydroxy chloroquine to the cancer patients might be beneficial as these drugs also has anti-cancer effects.

KEYWORDS

COVID-19, Cancer care, Cancer Incidence, Cancer trend, COVID-19 task force

INTRODUCTION

Coronaviruses belong to the family Coronaviridae in the order Nidovirales (1). They can be classified into four genera: Alpha corona virus, Beta corona virus, Gamma corona virus and Delta corona virus. Among them, alpha and beta corona viruses infect mammals, gamma corona viruses infect avian species and delta corona viruses infect both mammalian and avian species (2). The Life cycle of Corona virus infection begins when the viral spike (S) glycoprotein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor attached spike protein. Depending on the host cell protease available, cleavage and activation, allows the virus to enter the host cell by endocytosis or direct fusion of the viral envelop with the host membrane. On entry into the host cell, the virus particle is uncoated and its genome enters the cell cytoplasm. The corona virus RNA genome has a 5' methylated cap and a 3' polyadenylated tail, which allows the RNA to attach to the host cell's ribosome for translation. The host ribosome translates the initial overlapping open reading frame of the virus genome and forms a long polyprotein. The polyprotein has its own proteases which cleave the polyprotein into multiple nonstructural proteins (3).

A newly emerged human coronavirus (COVID-19) was reported in December 2019 in Wuhan, China (4). The Origin of this Corona viral infection is not known till date. This COVID-19 has spread to more than 210 countries of world. World Health Organization (WHO) has declared novCOVID-19 as pandemic disease on march 11 2020. Corona is a member of beta corona viruses like the Severe Acute Respiratory Syndrome Human Coronavirus (SARS H-CoV) and the Middle-East Respiratory Syndrome Human Coronavirus (MERS H-CoV). Until today, six different strains of Human coronaviruses (H-CoVs) have been reported, in addition to the newly emerged COVID-

19. 229E and NL63 strains of HCoV belong to Alpha corona viruses while OC43, HKU1, SARS, MERS and COVID-19 HCoV belong to beta coronaviruses (5). SARS and MERS H-CoV are the most aggressive strains of coronaviruses, leaving about 800 deaths each. SARS H-CoV has a 10% mortality rate, while MERS H-CoV has a 36% mortality rate, according to WHO (6).

Epidemiology of COVID19: All ages are susceptible but infection is severe in age less than 10 years and more than 60 years. COVID-19 is transmitted through droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic carriers. Transmission can also occur by touching the fomites which are contaminated by viruses and then touching the nose, mouth, eyes. Virus can be present on different surfaces of daily use from few hours to several days. They can survive on metal, glass and plastic for as long as nine days, unless they are properly disinfected. Some can even hang around for upto 28 days in low temperature. This may vary under different conditions (e.g. type of surface, temperature or humidity of the environment) (7). Studies have shown, higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people (8). The virus can remain viable on surfaces for days in favorable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc (9). The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization or feco-oral route is also hypothesized (10). As per current information, transplacental transmission from pregnant women to fetus has not been proven. However, neonatal disease due to post-natal transmission is described. The incubation period varies from 2 to 14 days [median 5-days] but positive cases are detected even after 30 days. Studies has identified

angiotensin converting enzyme-2 (ACE-2) as the receptor through which the virus enters the respiratory mucosa. Presently there are around 27 lakh COVID-19 positive cases Worldwide with more than 19,000 deaths. In India around 23,500 positive cases are detected out of which 722 death is reported as on April 23 2020. In Karnataka around 445 COVID-19 Positive cases is detected with 17 deaths till date, first death in India was reported at Kalburgi district of Karnataka.

Cancer care is challenging in the current COVID-19 crisis. At present, about 13 lakhs new cancer cases reported in India. In most of the Indian Cancer Registries, Lung cancer is predominant in males. There is an increasing trend observed in recent years in females (11). In Karnataka about 78000 cancer cases are reported every year (12). Many studies have already reported smoking as the main risk factor for lung cancer. The ACE receptors are seen in very high level in smokers, which is also the nidus for the corona viral infection.

Cancer care consists of Surgical, Chemotherapeutic, Radiotherapeutic management with pain, palliative and best supportive care for terminally ill patients. The treatment decision must be individualized with multidisciplinary approach after case discussion in multidisciplinary clinics. Each case must be evaluated thoroughly weighing the risk of COVID-19 infection versus benefit of cancer care in the present health emergency declared by Government of India. The optimum utilization of the limited human resources by keeping a reserve of health care professionals (HCP) as buffer must be done anticipating the next phases of pandemic outbreak in community. Best treatment modality possible should be given. Alternate modes of drug administration, metronomic chemotherapy regimens, hypo fractionated radiotherapy schedules must be planned without compromising the cancer out come to limit the risk of COVID-19 infection as majority of these cancer patients have low immunity and are highly susceptible to COVID-19.

MATERIAL AND METHODOLOGY

About 29 Population based cancer registry exists under the network of National Cancer Registry programme in India, majority of the registries exists in north east India. In South India, three population-based cancer registry exists locating and covering population of Bengaluru (BBMP), Chennai, Thiruvananthapuram. KMIO also has a Hospital Based Cancer Registry (HBCR) and more than one fourth cancer cases of PBCR is from the base Institution. There are 475 data sources, comprising cancer hospitals, general and private hospitals, teaching hospitals, pathology laboratories, city corporation death units and the city municipal death registration offices. The registry staff visit the sources and scrutinize the records kept in the medical records and pathology departments. COVID-19 Incidence, Guidelines for management of COVID-19 is obtained from Ministry of Health and Family Welfare, Government of India.

STATISTICAL ANALYSIS

Join point regression analysis was used to calculate the cancer trend and summarized by using Average Annual Percentage Change (AAPC). AAPC is a summary measure of the trend over a pre-specified fixed interval. It allows us to use a single number to describe the average APCs over a period of multiple years. It is valid even if the joinpoint model indicates that there were changes in trends during those years. It is computed as a weighted average of the APCs from the joinpoint model (11), with the weights equal to the length of the APC interval. Tabulation and graphs are used for descriptive analysis of COVID-19 Cases in Karnataka and India.

RESULTS

The number of cancer cases in India and Karnataka is given in table (1). The Incidence of COVID-19 Positive cases of India and Karnataka is depicted in Fig (2&3), there is an exponential rise in COVID-19 positive cases. With this increasing trend all over the country, the number of cancer patients getting infected is also high because of immunosuppression. In Karnataka, about 78,000 new cases are reporting every year. A population-based cancer Registry Bengaluru, registered around 11,000 new cancer cases with 126 and 157 Age adjusted rate per 1 lakh population in males and females respectively. Fig 4. depicts the cancer trend of both sex in PBCR, Bengaluru from 1982 to 2000 which observed that there was no trend (not significant increase or decrease) in AAR's for both sexes. After 2000, it observed 2.1 percent annual change in males and 2.2 percent annual change in females. Average annual percentage change (increasing cancer) for male cancers is 0.9% and 0.8% for females, a significant increasing

trend for both the gender is observed in Bengaluru PBCR (P-value<0.001). As like in most of the Cancer Registry of India, Lung Cancer is predominant site with Age adjusted rate 13 per lakh population in males and sixth leading site in females with AAR 6 per lakh population and in both males and female's lung cancer AAR showing Statistically increasing trend p-value<0.005 (Fig5).

DISCUSSION:

In the Institute firstly the COVID-19 Taskforce must be constituted with the nomination of Nodal officer who will be in touch with Health ministry and will update the recent guidelines day to day for better management of patients. Representatives from each department must be members of COVID-19 taskforce. They will sensitize the staffs about new updates regarding policies and decision making of COVID-19 task force in managing cancer care. Members of the COVID-19 taskforce will prepare Standard Operating Procedure (SOP) for smooth functioning of department which must be followed for optimal Oncologic care in the Regional Cancer Centre (RCC) to prevent cancer patients from COVID-19 infection. The Guidelines from Ministry of Health and Family Welfare (MOHFW), Government of India must be ideally followed in every Institute. The patient movement and exposure by stepping outside the house must be limited for recently treatment completed patients. The follow-up can be postponed after necessary communication with the patients by treating Oncologist.

The follow-up method should be done by optimum utilization of existing telemedicine unit. A separate Help line for Cancer care must be created and should function 24/7 where in all the queries raised by the patients and doubts must be answered and psychological support must be given by cancer care specialists. Video conferences (VC) can be arranged and instructions can be given to the patients by treating doctors. Triage must be done in categorizing cases for emergency procedures and SOP's of individual department must be followed. Oncologic emergencies must be dealt without delaying. Plan of action must be drawn anticipating an outbreak in the Institute. Informed Consent (ANNEXURE-I) must be taken from all the patients and attenders who are visiting the Regional Cancer Centre (RCC), regarding the risk of COVID-19 infection after explaining in detail in their own regional language they understand. All the Cancer patients must be evaluated and categorized based on the Tumor Node Metastasis (TNM) staging. All emergency treatments should be given without any delay. Bulk Short Message Service (SMS) must be sent to all Patients regarding the COVID-19 awareness and their scheduled cancer care treatment. In the Institute, Patients queries will be addressed using telemedicine/ dedicated helpline facility. For patients who are unable to travel to RCC, the local doctor service can be utilized via telemedicine. Based on the seriousness of the case, emergency patients can be referred to RCC for further course of action.

All patients and attenders (one attender per patient only) arriving to RCC must be considered as potentially COVID-19 infected and must undergo thermal screening at the entrance. A separate dedicated screening wing for COVID-19 symptoms which is away from the hospital services must be formed by COVID-19 task force. Even Cancer Screening Bus equipped with lab facilities can be used for this purpose. In case, any COVID-19 positive case is detected inside the hospital premises, then there is risk of many health care professionals being quarantined and even closure of hospital for sanitization which will affect hundreds of cancer patients availing treatment. Isolation ward with adequate number of beds must be set aside for patients who develop COVID-19 symptoms. Patients movement inside the hospital must be restricted by providing maximum bedside clinical services.

A. Surgical Oncology:

Emergency patients must undergo COVID-19 testing before being posted for surgical procedure. All planned surgeries for early disease can be postponed if feasible or other less invasive modalities of treatment having same local control rate and outcome must be carried out. If surgery is mandatory, then patient must be admitted well in advance considering the Quarantine period also for COVID-19 symptoms. Patients can be posted after quarantine period and confirming that the COVID-19 test result is negative. It is better to avoid Laparoscopy surgeries as there is increased risk of aerosolization and exposure to operating surgeons and OT staff in the highest level. Smoke evacuators must be used if electrocautery is used. Surgeries planned, must be completed in short time and surgical team must be minimized for reduced exposure. Elective cases can be posted for surgery after considering co-morbid conditions (Age, Hypertension,

Diabetic, Cardiac diseases, Respiratory disease, liver and renal failure cases) length of stay in hospital and Intensive care unit admission. It is best to avoid surgery in terminally ill and poor outcome patients, who can be treated by best supportive care. Guidelines of NHS, ASCO must be followed (13), along with Guide lines from Ministry of Health and Family Welfare Government of India.

B. Chemotherapy:

Patients who have already received 3 to 4 cycles of chemotherapy, can complete the treatment course after careful evaluation of Hemogram, Biochemistry. Shorter chemotherapeutic regimes must be considered wherever possible, oral chemotherapeutic agents are better than Intravenous administration as it reduces the risk of exposure by minimal hospital visits and better tolerability of patients. The risk of neutropenia must be tackled with colony stimulating factors. The cohort of high-risk patients susceptible to develop COVID-19 infection must be monitored carefully. The weekly Hemogram, Biochemistry reports can be discussed with doctors by telemedicine facility. If patient is COVID-19 positive during the course of treatment, then chemotherapy must be stopped and COVID-19 management must be initiated as per the severity of COVID-19 infection and clinical treatment guidelines must be followed. Allogenic Stem Cell Transplant (SCT) must be delayed in the wake of COVID-19 infection. In case, its absolutely necessary to undergo SCT, then Patient and Donor must follow the SOP framed by taskforce.

Many researches have already established the benefits of chemoprophylaxis drugs used in COVID-19 infection for health care workers (CQ, HCQ- Hydroxy chloroquine, Azithromycin). These drugs have anti-cancer benefits in lung cancer, glioma, pancreatic cancer, solid tumors, leukemia, multiple myeloma. They have direct anti-tumor action by P53 pathway, TLR-9, Nuclear factor Kappa-B (NF-kB) signalling pathway. They activate caspase-3 and modulate Bcl-2/Bax ratio during apoptosis in CLL, B-cell CLL and Glioblastoma. This drug has synergism with approved anti-cancer drugs like Doxorubicin, Daunorubicin, Mitoxantrone and other chemotherapeutic drugs (14-22). Till date, there is no published evidence on use of prophylactic anti-viral therapy for COVID-19 in patients during cancer treatment.

C. Radiotherapy:

Cases must be evaluated thoroughly. All emergency cases like Spinal Cord compression, Bleeding, Superior vena cava obstruction (SVCO) must be started at earliest. Consider single fraction wherever possible instead of 4-5 fractions. Patients must be admitted after COVID-19 evaluation and radiotherapy started. Select hypo fractionated regimes to reduce the hospital stay and visits (Example: Breast cancer). Brachytherapy treatment must also be completed in single application instead of multiple applications with time gap, thereby reducing the hospital stay of patients and risk of exposure. Stop radiotherapy, if patient becomes COVID-19 positive and take all necessary action to be treated in Dedicated COVID Health Centre (DCHC) or Dedicated COVID Hospital (DCH) depending on the severity of the infection. Patients waiting for radical radiotherapy must undergo COVID-19 screening and testing before initiating radiotherapy. Patient requiring Brachytherapy must be admitted after COVID-19 and pre-anesthetic clearance, as long delay will increase the overall treatment time affecting the local control rates and Overall Survival. Radiotherapy for Pediatric patients can be postponed as they are vulnerable group for COVID-19 infection, most of them also require anesthetic assistance to receive radiotherapy. Human resources management of anesthetists is very crucial in the pandemic crisis as they are also required in DCHC, DCH. Adjuvant treatment for border line risk group must be delayed. Patients must be on close follow-up to reduce the risk of recurrence. High risk group can receive adjuvant radiotherapy after COVID-19 clearance.

CONCLUSION: In the present Health emergency of COVID-19 crisis, Cancer care is being affected by this pandemic disease. Increasing trend is seen in cancer incidence in India and also in Karnataka. There is exponential increase of COVID-19 positive cases in India and Karnataka. Delay or long postponement in Cancer treatment will result in compromising local control rate and overall survival.

As most of the Cancer patients have low immunity, the risk of COVID-19 infection is very high as they are easily susceptible in one end and on the other hand, even a single COVID-19 positive case in the treatment

premises might end up with large number of health care professionals getting quarantined and closure of the affected area for sanitization which will affect many cancer patients treatment. So COVID-19 screening and testing must be done compulsorily before starting cancer treatment. Shorter treatment regimens with minimal human resource wherever possible must be considered. Chemoprophylaxis with hydroxy chloroquine to the cancer patients might be beneficial as these drugs also has anti-cancer effects.

Table1: Estimated Number of New Cancer cases based on Crude Rate (2020)

Region	Males	Females
India	622203	698725
Karnataka	34742	43639
Bengaluru	6200	7490

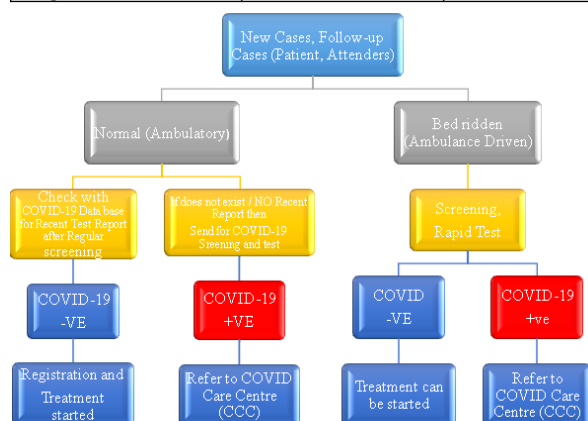


Fig1: Flow Chart: Work Flow to be followed by Cancer Patients attending Regional Cancer Centre for treatment in COVID-19 crisis

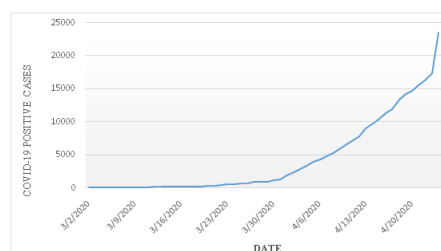


Fig2: COVID-19 Positive Cases Trend Over the Period in India

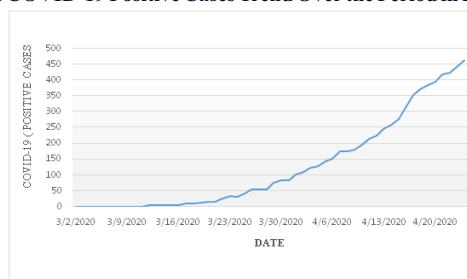


Fig3: COVID-19 Positive Cases Trend Over the Period in Karnataka

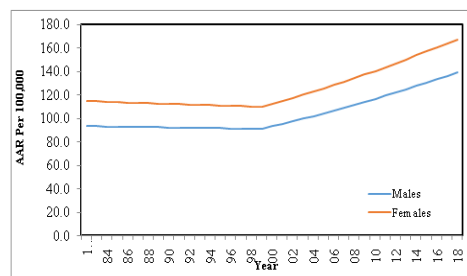
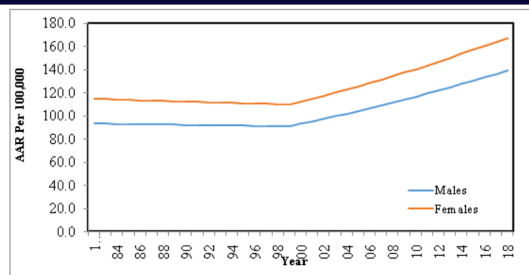


Fig4: Cancer Trend Over time: All Sites PBCR Bengaluru: (1982-2018)



ANNEXURE-I

Fig5: Cancer Trend Over time: Lung Cancer PBCR Bengaluru: (1982-2018)**Name of the Hospital:****Doctor's Name:****Date and Time:****DECLARATION**

During the current Corona Contagion (COVID-19) crisis, I have come to the Hospital all by myself as an Emergency Treatment. If, I am an asymptomatic carrier or an undiagnosed patient with COVID-19, I suspect that it may endanger Doctors and Hospital Staff, it is my responsibility to take all appropriate precautions. I will not spit in Hospital premises, will strictly follow respiratory etiquettes, maintain Social distance and good personal hygiene which has been explained to me by the hospital staff in prevention of COVID-19 infection and will follow all the Protocols advised by them.

I also know that, I may get an infection from the hospital or from a Doctor and I will take every precaution to prevent this from happening. I will not at all hold any Doctors and Hospital staff accountable if such an infection occurs to me or my accompanying persons endangering my life or others.

Patient's Sign/ Thumb Impression

Patient's Name:

Attender Name and Signature:

Mobile No:

Address

REFERENCES:

- [1] Enjuanes L, Almazan F, Sola I, Zuniga S. 2006. Biochemical aspects of coronavirus replication and virus-host interaction. *Annu. Rev. Microbiol.* 60:211-30.
- [2] Perlman S, Netland J. 2009. Coronaviruses post-SARS: Update on replication and pathogenesis. *Nat. Rev. Microbiol.* 7:439-50.
- [3] Simmons G, Zmora P, Gierer S, Heurich A, Pöhlmann S (December 2013). "Proteolytic activation of the SARS-coronavirus spike protein: Cutting enzymes at the cutting edge of antiviral research". *Antiviral Research.* 100(3): 605-14.
- [4] D.S. Hui, I.E. Azhar, T.A. Madani, F. Ntoumi, R. Kock, O. Dar, et al: The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health-the latest 2019 novel coronavirus outbreak in Wuhan, China *International Journal of Infectious Diseases*, 91 (2020), pp. 264-266.
- [5] J.F. Chan, S.K. Lau, K.K. To, V.C. Cheng, P.C. Woo, K.-Y. Yuen. Middle East respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease *Clin. Microbiol. Rev.*, 28 (2015), pp. 465-522.
- [6] M.G. Hemida, A. Alnaeem. Someone health-based control strategies for the Middle East respiratory syndrome coronavirus. *One Health.*, 8 (2019), p. 100-102.
- [7] Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med.* 2020.382:970-971. DOI: 10.1056/NEJMc2001737
- [8] Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med.* 2020.382:1177-1179 DOI: 10.1056/NEJMc2001737
- [9] Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. *J Hosp Infect.* 2020 Feb 6. pii: S0195-6701(20)30046-3.
- [10] Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet.* 2020.DOI:https://doi.org/10.1016/S0140-6736(20)30360-3
- [11] Time trends in Cancer Incidence Rates 1982-2010: National Cancer Registry Programme (ICMR). Bangalore, 2013.
- [12] Consolidated report of Population Based Cancer Registries 2012-14. Kidwai Memorial Institute of Oncology, Bangalore, 2018.
- [13] Talha Khan Burki. Cancer guidelines during the COVID-19 pandemic. *The Lancet Oncology.* April 2020.
- [14] Goldberg SB, et al. A phase I study of erlotinib and hydroxychloroquine in advanced non-small-cell lung cancer. *Journal of Thoracic Oncology.* 2012;7(10):1602-1608. doi: 10.1097/JTO.0b013e318262de4a.
- [15] Vogl DT, et al. Combined autophagy and proteasome inhibition: a phase I trial of hydroxychloroquine and bortezomib in patients with relapsed/refractory myeloma. *Autophagy.* 2014;10(8):1380-1390. doi: 10.4161/auto.29264.
- [16] Boone BA, et al. Safety and biologic response of pre-operative autophagy inhibition in combination with gemcitabine in patients with pancreatic adenocarcinoma. *Annals of Surgical Oncology.* 2015;22(13):4402-4410. doi: 10.1245/s10434-015-4566-4.
- [17] Chi M-S, et al. Double autophagy modulators reduce 2-deoxyglucose uptake in sarcoma patients. *Oncotarget.* 2015;6(30):29808-29817.

- [18] Sehgal AR, König H, Johnson DE, Tang D, Amaravadi RK, Boyiadzis M, Lotze MT. *Leukemia.* 2015 Mar; 29(3):517-25.
- [19] Zhang Y, Wang Q, Ma A, Li Y, Li R, Wang Y. *Oncol Rep.* 2014 May; 31(5):2298-304.
- [20] Balic A, et al. Chloroquine targets pancreatic cancer stem cells via inhibition of CXCR4 and hedgehog signaling. *Molecular Cancer Therapeutics.* 2014;13(7):1758-1771.
- [21] Kim EL, et al. Chloroquine activates the p53 pathway and induces apoptosis in human glioma cells. *Neuro-Oncology.* 2010;12(4):389-400. doi: 10.1093/neuonc/nop046.
- [22] Molenaar RJ, Coelen RJS, Khurshed M, Roos E, Caan MWA, van Linde ME, Kouwenhoven M, Bramer JAM, Bovée JVMG, Mathôt RA, Klumpen HJ, van Laarhoven HWM, van Noorden CJF, Vandertop WP, Gelderblom H, van Gulik TM, Wilmink JW. *BMJ Open.* 2017 Jun 10; 7(6): e014961.