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RADIOTHERAPY IN COVID-19: A REVIEW

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Abstract

The World Health Organization (WHO) stated the novel coronavirus (COVID-19) a global pandemic on 11th March 2020. The virus-infected patients suffered from a respiratory disease called Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-CoV-2). A proteinaceous exudate, alveolar edema, and hyperplasia associated with monocytes and lymphocytes alveolar inflammatory infiltration was observed in the affected patient's lungs. Virus broadens a systemic inflammatory reaction with a cytokine release syndrome which is characterized with the aid of using unexpected growth in many pro-inflammatory cytokines especially IL-6, IL-1, and TNF-α through activated M1 macrophage phenotype. Virus block IL-6 with tocilizumab and the usage of respirator device appears to be very vital. Radioactivity is the process by which unstable atomic nucleus losses energy by radiation, mainly using alpha, beta, and gamma rays. SARS-CoV-2 affected lungs can be treated by a low dose of radiotherapy. It was found that minute dose chest radiation therapy can be able to wean patients off a ventilator as it can reduce inflammation inside the lungs of severely infected COVID-19 patients. Numerous such clinical trials are underway and researchers may work to cure the COVID-19 lung infections by radiotherapy.

Keywords: *SARS-CoV-2, Virus, Radiations, Radiotherapy, COVID-19.*

Introduction

The first COVID-19 human infection was observed in December 2019, in China, and was due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus [1]. It infects the lungs by causing alveolar edema and may lead to lung cancer [2]. The unparalleled burden of SARS-CoV-2 globally is a big concern currently, COVID-19 affected people with cancer are more susceptible to the worse outcome of the disease and require ventilator support for survival [3]. The symptoms associated are cough, dyspnoea, fever, and lung lesions [4]. In the advanced stage, pneumonia progresses to acute respiratory distress syndrome and needs life-support to sustain the patient's life. The epidemiological survey has indicated that mortality rates are higher in the elderly population [5]. The virus has a life cycle of 5 steps: attachment, penetration, biosynthesis, maturation, and release. The virus interacts with the host receptors (ACE 2) (attachment) and penetrates the host cells by membrane fusion or endocytosis (penetration). Once the virus enters inside the cell, SARS-CoV-2 disassembles, proteins are removed and genomic RNA is released in the cytoplasm. Host cell machinery i.e. the ribosomes translates the RNA strand into pp1a and pp1ab proteins or viral polyproteins (biosynthesis). These proteins combine with genomic RNA and polymerase causes discontinuous transcription and releases subgenomic mRNAs and then translation occurs with viral proteins (maturation). In the Golgi apparatus and endoplasmic reticulum viral proteins assembles with genomic RNA into virions and then via vesicles get transported (release) [49]. Although current medical management is available no targeted therapy is there till now. In clinical trials, several drugs have been tested including hydroxychloroquine, lopinavir-ritonavir, remdesivir, azithromycin but none of them shown to be a definite therapy yet. Clinical trial testing on more therapies is still going on [5].

Carcinogenesis is a multistage process that involves deregulation of various biochemical and physiological cascades that controls cell growth, survival, and apoptosis. The main therapeutic option for cancer patients is radiotherapy, it offers quality and raises the standard of living [50]. Radiotherapy can inhibit the growth rate of cells and this approach can be an utmost against COVID-19. The use of UV or gamma radiation for sanitation and sterilization can be another strategy [22]. By using this therapy virus transmission can be controlled. In response to the ongoing pandemic, suggestions concerning radiotherapy usage in cancer treatment may decrease the risk of viral spread. When compared to other treatments radiotherapy or chemoradiation has gained outstanding outcomes under normal conditions [51]. Clinical trials are still going on low doses of radiotherapy (30 to 100 cGy) in COVID-19 patients. It could decrease the inflammation and block the cytokine storm thereby mitigating the pneumonitis severity [52]. Studies are designed to know the feasibility and clinical outcomes of low radiation therapy dose (70 cGy in a single fraction) in COVID-19 patients with pneumonia [6]. Based on data analysis from the early outbreak the total cases are 142,191,658 and a total of 3,035,686 mortalities have been reported while making this review.

Structure of Coronavirus

The Coronavirus is a single-stranded positive-sense RNA virus having nucleoprotein covered by a matrix protein named capsid and is circular or pleomorphic in structure [Fig. 1]. The viral genome contains many unique N-terminal fragments within the spike protein [7]. Coronavirus major genes consist of S, E, M, and N proteins. There are mainly two polypeptides, one is pp1a and another one is pp1ab. All the proteins transcript from the single-strand RNAs and has a similar structure. There are minute NH_2-terminal domains present external part of the virus and the long-chain COOH is present inside the virion [8]. Polyproteins pp1a and pp1ab changes into non-structural protein by two protease 3CLpro and PLpro by open reading frame 1. During Covid 19 infection the non-structural proteins play a beneficial role in the transcription and replication progression [9-12]. The replication and the transcription of the coronavirus genome take place at cytoplasmic membranes which help both continuous and discontinuous RNA synthesis. The proteases play a significant role and reduce the polyprotein into the functional pieces. Those protease helps in viral replication and thus can be a

potential drug target to block the virus spread [13,14].

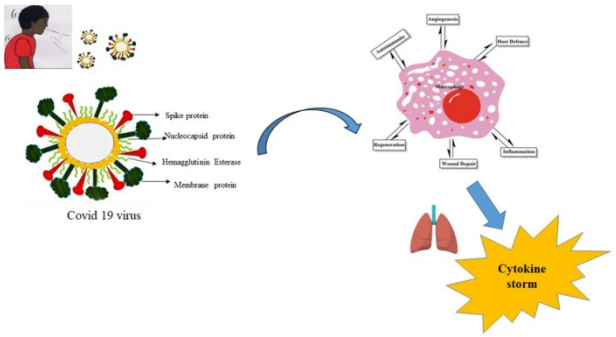

Figure 1. COVID-19 proteins associated with macrophages stimulation and release of the cytokine storm.

Hyper inflammation due to severe COVID-19

Severe patients who showed an increase in pro-inflammatory cytokines were rushed to the hospitals for intensive care [15, 16]. SARS-CoV-2 produces ARDS with severe pneumonia. High levels of inflammatory mediators, neutrophil to lymphocyte ratio were found to be elevated in the blood of the patients. Activated macrophage increases the cytokines production like IL-7, IL-6, and tumor necrosis factor (TNF). The excess secretion of IL-6 may produce more sera in the patient. The IL-1β and IL-18 have an important role in COVID-19 inflammation [17]. The coronavirus in the global T cell affects CD8+ T cells and produces severe disease, but the potential mechanism is still not clear. So IL- receptors and IL-1β blockade will be helpful to combat COVID-19 in the affected patients [18]. COVID-19 patients have shown CCL2 and CCL7; chemokines bound with the CC-chemokine receptor 2-positive monocytes in Bronchoalveolar fluid (BALF). The BALF has single-strand RNA sequencing which produces severe disease [19]. The CD8+ T cell works as a memory cell and the T cell gene is the main cause of the severe disease in the BALF affected patient. COVID-19 can be destroyed by the drug which affects the T cell rapidly [18].

Respiratory effect of COVID-19

There are a lot of nucleotides (approx. 29727) among them 265 and 342 are localized in the 5' and 3'nontranslated regions. There are two large 5'-terminal open reading frames, such as 1a and 1b which are required for viral RNA synthesis [13]. The other twelve ORFs are encoded by structural proteins such as S, M, N, and E and the remaining proteins infect the host. After entering the host cell at first viral S protein bind with the receptors changing their structure and forms typical spikes having the shape of the petal on the virion surface damaging the respiratory system [13] [Fig 2].

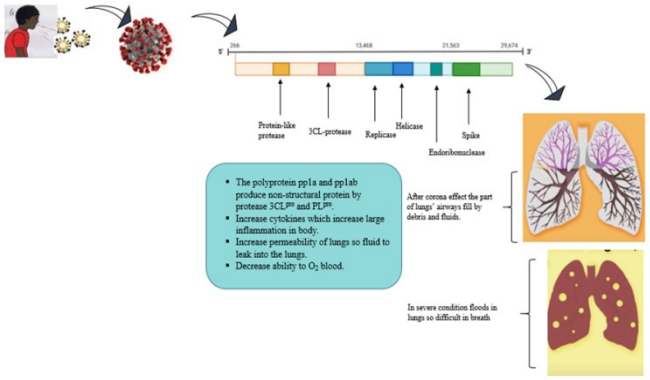

Figure 2. Effect of Coronavirus in lungs.

Radiotherapy in COVID-19

Radiotherapy in the present pandemic situation is a provoking idea for the eradication of the corona virus and managing the disease condition. Radiation has a key role in alleviating overall patient survival [22]. The growth of the malignant tumor can be controlled by radiation to a higher level by cell apoptotic mechanism. The radiation therapy can be used for suppressing the COVID-19 associated cells by minimum dose delivery. COVID-19 targets the respiratory system causing breathing problems and it aggregated in the lungs [20]. The diagnosis of the patient can be achieved with some appropriate imaging modality. According to the condition of the patient future treatment, strategy can be generated and executed [20-22]. Studies reported that ionizing irradiation causes DNA damage and stimulates cellular stress response. Another study evidenced γ-IR and X-ray radiation causes DNA abrasions and also break the double strands resulting in the activation of NHEJ machinery which is linked with increased activity of multiple cellular factors participating in transcription and stimulation of NF-κB, HAT1, Sp1, and CBP/p300 which leads to SWI/SNF-regulated chromatin remodeling [23]. For cells infected by HIV, both X-ray and γ-IR stimulate

NF-κB DNA binding and result in apoptosis via chromatin DNA damage [24]. Other studies indicated that human colonic carcinoma cells when treated with the X-ray stimulate NF-κB-mediated ultimately leads to cell death [25].

Radiotherapy has been a widely effective anti-inflammatory treatment since the early 20th century [22, 26]. It has an important role in cancer treatment such as cervical, vaginal and vulvar cancers, etc. [23, 27]. Clinical observation states that COVID-19 patients suffered from compromised immune response resulting in quick virus spread and causing damage to the lung tissues, further leads to the activation of macrophages and granulocytes. Low-dose radiation causes macrophage (M1 and M2) polarization resulting in anti-inflammatory responses [28]. Since ancient times, low-dose radiation employed for the cure and treatment of different infectious diseases like pneumonia [29]. Scientists from America and Iran during March 2020 introduced the use of low-dose radiation therapy (LD-RT) for COVID-19 pneumonia patients [30]. Afterward, Canadian, Spanish, French, and German scientists also started following this approach. The suggested dose ranges between 100– 1000 mGy for lungs, thus could be a helpful therapeutic option for chronic pneumonia in COVID-19 patients [31]. LD-RT has an important role as an anti-inflammatory hence LD-RT can be used against respiratory problems associated with COVID-19 patients. High-dose radiation therapy produces pro-inflammatory mediators in immune and endothelial cells. The LD-RT produces anti-inflammatory action by blocking the interaction among leukocytes and endothelial cells [24]. This suppresses the release of inflammatory mediators and macrophages decreases the levels of TNF-α, beta, and IL- 1 secretion. The adjunctive radiotherapy can be used for the treatment of COVID-19 [24, 32]. Radiotherapy downregulates the working of macrophages and shows an anti-inflammatory effect. Radiotherapy reduces viral RNA transmission and can cure the virus-affected cells. This therapy alters the inflammatory state of the lungs of SARS-CoV-2 pneumonia patients. But LD-RT is associated with adverse effects as long-term radiation leads to diseases, such as cancer [25, 33] [Fig. 3]. Furthermore, a minute dose of ionizing radiation is associated with the cytokine apoptosis of infiltrating cells, as symptoms were improved within hours. Furthermore, autopsies reports of the lungs have indicated the presence of many microthrombi in COVID-19 patients [34, 35].

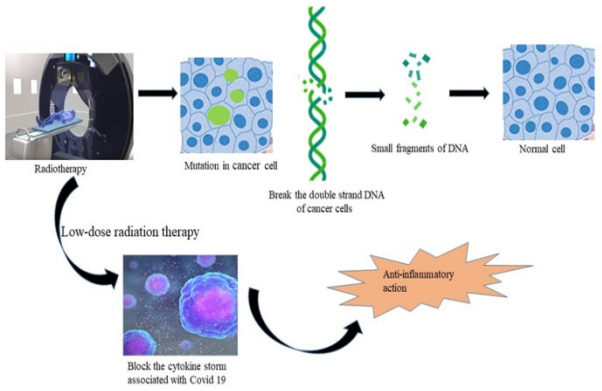

Figure 3. Radiotherapy in cancer and Covid-19

Coping with the COVID-19 outbreak, the main indications for the use of radiation therapy according to the published guidelines are shown in Figure 4. However, as time is going on the main thing is to emphasize some sort of treatment modification rather than delaying or postponing. In patients infected with COVID-19, previously ongoing treatments are not discontinued, radiotherapy is not initiated, till the patient has two negative PCR tests and becomes symptom-free for 14 days. Radiotherapy is important for the patient having cord compression. In such conditions, radiotherapy is recommended at the last shift so that the probability of virus exposure to other patients is minimized [7].

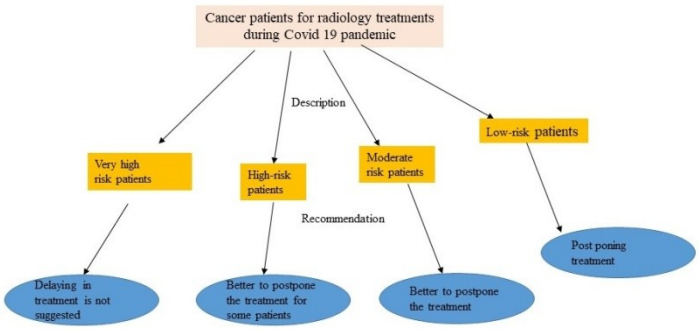

Figure 4. Categorization of cancer patients for radiology treatments during COVID-19 pandemic

All the facilities should be appropriately sanitized after the treatment. During radiotherapy, if suspicion of COVID-19 infection exists, the treatment must be discontinued till all the confirmatory tests are completed. In case of alteration in RT treatment, the preference will be given to hypofractionated regimens over conventional. For example, short-course radiotherapy can opt-in rectal cancer followed by sudden or delayed surgery [36]. Hypo fractionated full breast irradiation is one more good example of facilitating limited breast irradiation for competent applicants [37]. For prostate cancers the full pelvis radiation is not required, use of the stereotactic body or a 19-Gy-fraction of increased dose radiation therapy can be adopted. Instead of using a conventional schedule desperately, opting for reduced time-consuming techniques to minimize patient manifestation and staff load should be given priority. For example, 3D conformal RT and IMRT have minute differences thereby preference should be given to 3D.

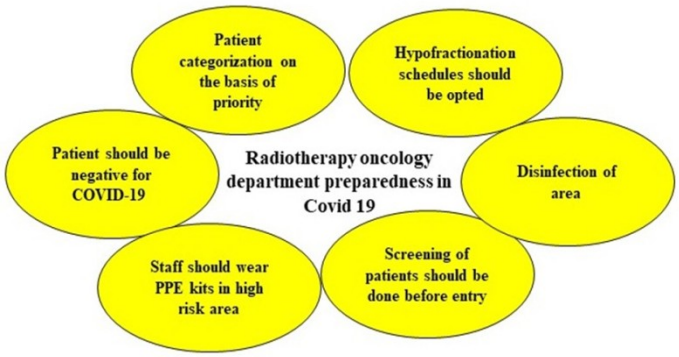

Figure 5. Radiotherapy oncology department preparedness in COVID-19

It is highly advised to follow virtual techniques in radiation oncology departments during a pandemic by using social networking applications. In the current scenario of the COVID-19 crisis, institutional protocols constructed on logistics and priorities must be followed for the safe distribution of radiation therapy [38] [Fig. 5].

Previous literature has evidenced that a prolonged radiotherapy time linked with enlarged radiotherapy intrusion could lead to the increased overall survival rate of cancer patients [39–43]. Therefore, during the COVID-19 pandemic radiotherapy oncology department is facing serious issues as there is a risk of infection transmission to staff members [44]. Moreover, many radiotherapy centers are located in basements and the gathering of patients rises the infection risk. Therefore, enhanced requirements are need of the situation for COVID-19 protection in both patients and the medical staff. During the COVID-19 outbreak, hospitals and many radiotherapy centers have executed multiple techniques for the protection and prevention of patients and staff. Firstly, the appointments of specialized preventive taskforces taking care of clinical operation management both at the hospital and departmental levels. Staff rotations, screening of patient before admission and personnel COVID-19 training was preferred. Various modifications were made including radiotherapy center zoning was executed. Personnel working should wear corresponding PPEs kits. Proper strategies were implemented for disinfection and waste disposal. Thus these alterations in radiotherapy oncology departments in unprecedented health crisis may stop the spread of the virus [53].

In the pandemic situation, the radiotherapy departments are divided into three zones according to the basis of risk of contaminations such as Clean area (very low risk of contamination), semi-contaminated area (contamination probability is medium), and contaminated (high risk of contamination). The COVID-19 affected lung cancer patients can be treated by the combination of radio and chemotherapy protocols [45]. Radiotherapy can also be a treatment for pancreatic cancer (PC) patients. For this treatment, shorter radiotherapy is performed. As in the pandemic situation, all the hospitals have suspended the surgery, so radiotherapy may be helpful as the short radiotherapy reduces the hospitalization of PC patients. For the safety of the patients, carbon ion radiotherapy (CIRT) is used to treat the PC. The main advantage of CIRT is that it will do less damage in the surroundings of the tumors. This type of treatment decreases the size of the tumor, lymphatic involvement and improves the rate of rescuable [46]. Radiotherapy has no side effect due to its target specification and the less time-

consuming treatment than immunology and chemotherapy [28, 47]. Considering patient safety in the pandemic situation, radiotherapy can be a safe approach as there is a minimum risk for the spread of the virus among the staff and the health caretakers [29, 48].

Conclusion

Many in vitro and in vivo evidence have indicated a significant rise in viral uptake and spread following irradiation. Furthermore, induction of apoptosis via ionizing radiation to the cells infected by the virus may stop the virus spread and growth of the disease. Due to the insufficient expertise about radiation beams and their consequences future experiments are needed for better outcomes of these radiations as well as the combination of radiations with antiviral drugs ("shock and kill" strategy). Paying attention to the discussed strategies might accelerate the spread of the pandemic.

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