

Low Dose Radiotherapy (LDRT) Can Be an Option For Curing COVID-19?

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Abstract

In December 2019, the epidemic of Coronavirus Disease 2019 (COVID-19) broke out in Wuhan in China. Symptoms of COVID-19 are non-definite and mild symptoms include: fever, cough. However, elderly and populations with comorbidities such as diabetes, hypertension are more likely to be at risk of severe pulmonary infection and death. Many therapies have been proposed and assed for treating (COVID-19). In April 2020, two papers appeared that suggested clinical trials of low dose radiotherapy (LDRT) for COVID-19 pneumonia. Following that, some researchers carried out some studies, and they modify the amount of doses and fractionation. Regarding the aging, some study using a sensitive age that ranged from 18 to 50 years, are more likely to have stochastic effects that cannot analyzed directly as it needs more time to experience these effects. In this review, we analysis the possibility of a low dose radiotherapy that can have in treating COVID-19 pneumonia, by using almost all accessed publications that performed on a low dose radiotherapy (LDRT) for curing bacteria or virus as well as studies that focus on using LDRT for anti-inflammatory. We show that LDRT can perform the mitigation and the repair response of the immune system to provide a potential therapy of COVID-19. A single dose of low-dose radiotherapy can be effective in both cost and time and could potentially relieve symptoms of respiratory rapidly. However, such treatment would not be without obstacle and it can be difficult since it is necessary to recognize those few patients who are more benefit from radiation treatment and identifying short and long-term impacts. clinical stage of disease should be known. Additionally, it is not acceptable to report that LDRT would be superior to any type treatment that are currently under taking, until results from clinical trial will be released.

Key words: Radiotherapy, COVID-19, Low dose, Pneumonia, Radiation

Introduction

In December 2019, the epidemic of Coronavirus Disease 2019 (COVID-19) broke out in Wuhan in China. From December to January of the outbreak, they reported 360 fatalities, over 16,000 confirmed cases, and more than 20,000 suspected cases in China. In

February 2020, the cases peaked ^{1,2}. After locked down nearly 60days, the reported cases deceased in Wuhan. On the other hands, in March, COVID-19 has elevated the world over 118,000 cases and 4291 deaths in 114 countries³. There were more than 6.6 million infections and more than 391,000 deaths worldwide⁴. Symptoms of COVID-19 are non-definite and mild symptoms include: fever, cough. However, elderly and populations with comorbidities such as diabetes, hypertension are more likely to be at risk of severe pulmonary infection and death⁵. Treatment of those patients who have COVID-19 pneumonia is a priority to decrease mortality which accounts about 5%⁶. Most treatment options focus on existing drugs, such as the anti-inflammatory

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drug dexamethasone, while the main treatment for most patients hospitalized with COVID-19 is supplemental oxygen⁷. Various historical cohort studies reported that a low dose radiotherapy can be provided to treat virus and bacteria^{8,9}.

In early April 2020, two papers by (Ghadimi-Moghadam et al. 2020 and Kirkby and Mackenzie 2020a) appeared that suggested clinical trials of low dose radiotherapy (LDRT) for COVID-19 pneumonia using low-linear energy transfer (LET) radiation exposure. This treatment was asserted that to constitute very low risk to patient health and avoid normal tissue toxicities. Subsequently, Ghadimi-Moghadam et al. suggested a low dose of radiation in ranged of mGy to lung, allowed by a single dose of 0.1, 0.18 or 0.25 Gy could be used to curing COVID-19 pneumonia (the selected dose was 0.25 Gy. This is because this amount is less than the dose that people received from natural background radiation in Ramsar, Iran which is about 0.26 Gy)^{10,11}. These suggestions were based on an earlier review by Calabrese and Dhawan in 2013. Also, in another article that provided by Salomaa et al, they suggested and evaluated a low dose radiotin therapy on viral pneumonia. This study was based on available information before 20 April 2020¹¹. In this review, we analysis the possibility of a low dose radiotherapy that can have in treating COVID-19 pneumonia, by using almost all accessed publications on a low dose radiotherapy (LDRT) for curing bacteria or virus as well as studies that focus on using LDRT for anti-inflammatory.

Historical Evidence

A study by Calabrese and Dhawan published in 2013, they reviewed 19 papers, mostly case reports, related to the outcomes from low dose radiotherapy for pneumonia. The study started from 1905, three papers were between 1905 to 1916, others were between 1925-1943. Similarly, Schillinge reported that x-ray in a range of diagnosis would be useful in treatment of certain infection¹² as well as mastitis, abscesses, ankylosing spondylitis, psoriasis, panaritium ossale, eczema, actinomycosis, paronychia, otitis, sinusitis, arthritis, pneumonia were treated with low dose x-ray¹³. In addition to that, there were three radiobiological studies assessed using radiation, Fried in 1941 performed using a guinea pig model, Lieberman

et al. in 1941 carried out study using a canine model and Dubin et al, in 1946 using a murine model, the first two of these for bacterially generated pneumonia and the last one virus generated pneumonia. The positive effect of radiation was appeared only in study that carried out by Lieberman et al. in 1941¹⁴.

Mechanism of action

Participation of the immune system in the pathogenesis of COVID-19 might also seem contradictory in point of view of the high mortality rate in those with fundamental conditions and of older age, who are often considered to be 'immune suppressed'. the depth of penetration of the virus in the respiratory tract can dictate susceptibility. However, sometimes patients may have difficulty restoring redox balance as a consequence of underlying condition rather than lacking immune function, generating in excessive pro-inflammatory cytokine cascades that drive disease pathogenesis. It is reported that T lymphocytes are hyperincite in COVID-19, and cells of the Th17 phenotype include: CD4+ and cytotoxic CD8+ cells¹⁵. T cells are major generator of pro-inflammatory chemokines and cytokines, that give a response to orchestrate to perform proliferation, infiltration, recruitment and in especially by myeloid cells that may aggravate the disease. It has been reported cytokine release storm in COVID-19 but at lower levels¹⁶. Based on this, pro-inflammatory cytokines are appearing as promising targets for therapeutic intervention, with IL-6, IL-1 β , IFN- γ , TNF- α , and GM-CSF being key players.

The basic assumption for LDRT action is that x-rays may generate anti-inflammatory phenotypes that could possibly support abate the cytokine storm that is common at end stage pneumonia¹⁷. Historical studies ranged dose of between 0.35 and 0.5 Gy to achieve an optimal result, while higher doses may result in increased inflammation¹⁸. Particularly, a dose of 1 Gy per fraction with six fractions to 6 Gy total is being used constantly to treat a range of mild inflammatory conditions¹⁹.

Low dose radiation in treatment of COVID -19

Ionizing radiation just not limited to treat cancers but also have been used treat various non-cancer diseases, including bacterial or viral pneumonia. Low

dose radiation can not only palliate inflammation and facilitates healing by performing the polarization of macrophages to an anti-inflammatory or M2 phenotype², but also causes apoptosis in radiosensitive neutrophils and activates T cells. In addition, LDRT reduced expression of molecules for cell adhesion, generate anti-inflammatory mediators like IL10 and transforming growth factor beta 1 (TGF- β 1), elevates apoptosis, and secondarily decrease leucocyte-endothelial cell interaction and vasodilation by obstructing the expression of producing nitric oxide synthase (iNOS), that is responsible to decrease nitric oxide levels^{20,21,22}. Additionally, low-dose radiotherapy can contribute to hyper-radio-sensitivity, further enhancing apoptotic death²². Likewise, Ghadimi-Moghadam reported the benefits of LDRT over therapeutic methods such as those that use antiviral drugs.

When the treatment causes in damage viral, therefore, this results in no viral genomes successfully replicated. However, When the treatment is not sufficient; thus, some genomes replicated. In addition, it is reported that LDR can result in regulation of lymphocyte counts and this leading to controls bacterial co-infections in patients who have COVID-19¹⁰.

Regarding the amount of the dose that being used, increasing the dose to equal or greater than 200 cGy are more likely to exert pro-inflammatory effects, activating some toxicities as reported in radiation therapy; thus, low doses (<100 cGy) is being suggested to simulate anti-inflammatory properties²³ such as reducing levels of pro-inflammatory cytokines like IL-1b²⁴, and inhibiting leukocyte recruitment [25]. This agree with a study that reported low doses X-rays in range kilovoltage can decrease pneumonia mortality from nearly 30 % to 10% on average²⁶ and the suggested doses were less than 100 cGy that alleviate the symptom in hours^{27, 28}. Similarly, studies on animals' models suggested that low dose radiation therapy (LDRT) could decrease the acute phase of pneumonia by 50%²⁹. Kirkby and Mackenzie reported the required dose to lung for a patient with COVID-19 pneumonia would be ranged from 30–100 cGy, and it is possible to relieve the life-threatening symptoms, can be delivered to the patient through conventional megavoltage radiation therapy⁸.

The stage of disease should be known before initiating treatment. It has been investigated that efficacy can increase if radiation was given early³⁰. This was explained by a study that use 105 patients with acute lobar pneumonia received a 50% erythema dose, and they noted that in the late stage, LDRT can resulted in spread diseases instead of controlling³¹. This was similar to a study by Desjardins stated that Roentgenotherapy ineffective if the pneumonia discharge was arranged³². One possible benefit of LDRT over other approaches would be that it can perform broadly, potentially impeding with several inflammatory, pro-oxidant pathways at multiple levels, compared to drugs that can only target a single cytokine³³.

Risk of induced cancer after LDRT

The doses that are supposed to use to treat COVID-19 is lower than the dose that inducing deterministic effects. However, according to epidemiological and experimental studies, doses approximately 100 mSv or less can resulting in incurring cancer¹⁴. Even though the induction of cancer for LDRT is anticipated to be small, they still must be assessed. In a study by García-Hernández et al. they evaluated the risk of cancer induction that associated with low dose radiation therapy (LDRT), for curing of immune-related pneumonia generating through COVID-19 infection. Female and male computational phantoms were used, a peripheral dose model and treatment planning system calculations was performed to determine the value of equivalent dose in each organ. Radiochromic films was used to approximate the skin dose, radiation protection approached were performed to evaluate and calculate the effective dose and the lifetime attributable risk of cancer. They reported that the doses outside treatment filed was very low that accounted for less than 0.06 cases per 10,000. However, the risk of cancer induction with such organ would evaluate with caution as they are more radiosensitive and partly or completely within the treatment fields, that results in an increase the risk of inducing cancer (for dose range from 1 to 10 mSv/cGy). Treating Female patient with low dose radiotherapy (with a dose of 100 cGy), aged 50 years, risk of cancer induction is 40%. Therefore, based on this study, it is impossible to report that stochastic effects are insignificant for low dose radiation therapy

for curing COVID-19, especially for young women³⁴. However, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) reported that radiogenic lung cancer is more in adult than children as adults more sensitive to LDRT therefore the correlation between age and radiogenic lung is not clear yet³⁵.

In addition, the risk of cancer induction of low dose ionizing radiation was estimated on cardiac CT angiography, the risk of cancer induction for lung cancer was 0.11% for female and 0.04% for male³⁶. Similarly, according to Zhang et al. 2020 females are more likely to be at higher risk of radiogenic lung cancer and breast cancer compared with male, but this opposed to mortality risk following COVID-19. Therefore, female patients are less likely to treat with low dose radiation therapy as they can experience more risk³⁷.

In another study, a kilovoltage cone beam CT (CBCT) were used for pelvic tumours. The estimations of inducing cancer risk are higher than the two previous articles, which was 4% for colon³⁸.

Studies and ongoing clinical trials on LDR for Covid-19

The biological studies by Salomaa et al., and Kefayat and Ghahremani as well as case reports that reviewed in Calabrese and Dhawan studies showed that cytokine storm cannot be controlled through anti-inflammatory impacts of LDRT, the immune system disrupted radiation due to this disruption may delay virus destruction^{11,39}. Kefayat and Ghahremani also reported that high viral load can have impact on the outcome of treatment therefore, in the presence of viral load, lung does not consider as the target organ, instead of that total body serve as the target organ and the LDRT would be more effective in treatment of COVID-19 pneumonia. They also assumed that the risk that associated with LDRT was constrained just to radiogenic pneumonitis, while Kirkby and Mackenzie assumed that the risk of LDRT for COVID-19 pneumonia may be very small^{11,8}.

Regarding the amount dose, Lara et al. reported that doses of 0.5Gy to lung can be cost-effective; this was based on nontoxic, anti-inflammatory treatment. They showed that the cytokine storm activated by interleukin 6 (IL-6) in COVID-19 pneumonia, demonstrated

that lung LDRT can act as an anti-IL-6 treatment⁴⁰. It expressed the LDRT as solid management and therapy of disease⁴¹. Likewise, Dhawan et al. uses a dose of 0.3 or 0.5 Gy to chest, the results showed a single dose at that range can result in alleviate symptoms. This was verified, based on an anti-inflammatory feature of LDRT⁴². This finding was come from Calabrese and Dhawan reviewed literature on the experimental studies on anti-inflammatory effects of LDRT, and on the anecdotal studies on LDRT for bronchial asthma and viral or bacterial pneumonia¹⁴. In addition, Rogdel et al showed that exposed entire lung with LDRT with a single dose of 0.5 Gy can justify clinical investigation. However, lung function tests and clinical markers (e.g. IL-6) should be determined to justification.

Another study contacted that exposing lung to a single dose of 0.8Gy, the number of patients were 15 aged at 18 years old, other than the radiation therapy, they receive several drugs ("lopinavir/ritonavir, hydroxychloroquine, azithromycin, piperacillin/tazobactam, low molecular weight heparin, corticosteroids, and tocilizumab") after 2, 5, 7 days patients' blood tested and the level of IL-6 measured. acute toxicities performed using the Radiation Therapy Oncology Group (RTOG) scales after one and three low dose radiation therapy⁴³.

Iran also performed clinical trial on low dose radiation therapy for COVID-19 pneumonia, the study was carried out at Shahid Beheshti University of Medical Sciences, the dose was 0.5-1 Gy. second dose delivered after 72 h; both lungs exposed. To measure acute toxicities IL-6 level used, number of patients was 5, aged 60 years and performed after one and four, seven days of low dose radiation therapy and at days 1, 7, 14 and 28 patients exposed to radiation dose from chest CT scan⁴⁴. In Italy, an arm pilot study contacted on LDRT for COVID-19 pneumonitis, number of patients was 30, aged 50 years, both lungs exposed, the dose was 0.7Gy. the level of IL-6 measured. acute toxicities performed using CTCAE v5. After phase phase II study, the phase I will be performed⁴⁵.

These trails were based on suggestion by Kirkby and Mackenzie. However, some researchers modify the number of doses and fractionation not follow the suggested amount. Regarding the aging, some study

using a sensitive age that ranged from 18 to 50 years, are more likely to have stochastic effects that cannot be analyzed directly as it needs more time to experience these effects. A model was performed in 2012 by Little for Japanese atomic bomb survivors to estimate the low dose that can have on the surrounding organs of lung, a dose of 1 Gy to lung can receive to heart that may result in with 8.5 extra deaths in early ages⁴⁶.

Conclusion

In conclusion, LDRT performed the mitigation and the repair response of the immune system to provide a potential therapy of COVID-19. A single dose of low-dose radiotherapy can be effective in both cost and time and could potentially relieve symptoms of respiratory rapidly, supporting in decrease mortality without potential long-term impacts. Sequentially, this can result in an early discharge from hospital and decrease cost of in-patient hospitalization. However, such treatment would not be without obstacle and it can be difficult since it is necessary to recognize those few patients who are more benefit from radiation treatment and identifying short and long-term impacts. clinical stage of disease should be known. Additionally, it is not acceptable to report that LDRT would be superior to any type treatment that are currently under taking, until results from clinical trial.

Ethical Clearance: Ethical clearance was not necessary as it was a review which included only collection of data.

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