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Low-dose Radiation Therapy in the Management of COVID-19 Pneumonia (LOWRAD-Cov19). Final results of a prospective phase I–II trial

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Abstract

Background and purpose: To evaluate the results of low-dose radiation therapy (LD-RT) to lungs in the management of patients with COVID-19 pneumonia.

Material and methods: We conducted a prospective phase I–II trial enrolling COVID-19 patients ≥50 years-old, with bilateral lung involvement at imaging study and oxygen requirement (oxygen saturation <93% on room air). Patients received 1 Gy to whole lungs in a single fraction. Primary outcome was a radiological response assessed as severity and extension scores at days +3 and +7. Secondary outcomes were toxicity (CTCAE v5.0), days of hospitalization, changes in inflammatory blood parameters (ferritin, lymphocytes, C-reactive protein, d-dimer and LDH) and SatO2/FiO2 index (SAFI), at day +3 and +7. Descriptive analyses were summarized as means with standard deviation (SD) and/or medians with interquartile ranges (IQR). A Wilcoxon sign rank test for paired data was used to assess the CT scores and Chi Square was used to assess for comparison of categorical variables.

Results: Forty-one patients were included. Median age was 71 (IQR 60–84). Eighteen patients (44%) previously received an anti-COVID treatment (tocilizumab, lopinavir/ritonavir, remdesivir) and thirty-two patients (84%) received steroids during LD-RT. The extension score improved significantly (p = 0.02) on day +7. Mean baseline extension score was 13.7 (SD ± 4.9) with a score of 12.2 (±5.2) at day 3, and 12.4 ± 4.7 at day 7. No differences were found in the severity score. SAFI improved significantly on day +3 and +7 (p < 0.01). Median SAFI on day 0 was 147 (IQR 118–264), 230 (IQR 120–343) on day +3 and 293 (IQR 121–353) on day +7. Significant decrease was found in C-reactive protein on day +7 (p = 0.02) and in lymphocytes counts on day +3 and +7 (p = 0.02). The median number of days in hospital after RT was 11 (range 4–78). With a median follow-up of 60 days after LD-RT, 26 (63%) patients were discharged, 11 (27%) died because of COVID respiratory failure and 4 (10%) died of other causes.

Conclusions: LD-RT is a feasible and well-tolerated treatment that could lead to rapid clinical improvement. Large randomized trials would be required to establish the efficacy of LD-RT to treat COVID-19 pneumonia.

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mental studies [10,11] found that LD-RT regulates lung inflammation and shifts macrophages towards an anti-inflammatory profile (increasing IL-10 and decreasing pro-inflammatory substances such as interferon gamma and IL-6). These results provided preclinical support for clinical trials. Several phase I/II studies of LD-RT for COVID-19 pneumonia have been published in the last year, proposing LD-RT as a safe and potential beneficial treatment [12,13].

We present final results of our trial Low-Dose Radiation Therapy in the Management of COVID-19 Pneumonia (LOWRAD-Cov19).

Methods and materials

Eligibility criteria included age ≥50 years, diagnosis of COVID-19 confirmed by PCR, bilateral lung involvement at imaging study (ground-glass opacities and/or consolidations) and oxygen requirement (oxygen saturation ≤93% on room air), all consistent with moderate-severe disease. Eligible patients, previous provision of written informed consent, were enrolled in a prospective single-arm trial (Clinical Trial Registration Number NCT04420390). The protocol was approved by our institutional review board and ethics committee. The study design and treatment details have been previously reported [14]. Briefly, patients were treated the same day of consent after undergoing a CT simulation. Planning target volume (PTV) was generated adding 1 cm cranial, antero-posterior, and lateral, and 2 cm caudal to both lungs. Heart and oesophagus were contoured as organs at risk retrospectively. Dose prescribed was 1 Gy, treatment was delivered through 2 opposite antero-posterior beams with multileaf collimator when appropriate. Planning goals were 80% of the dose received by > 95% of the PTV volume and maximal dose (\(D_{95\%}\)) < 115%.

Primary outcome was radiological response assessed as severity and extension scores [15–18] at days 0, +3 and +7. Image analysis was performed using the institutional digital database system (IMPAX 6.5.33, Agfa-Gevaert N.V.) by a resident of radiology and supervised by an experienced cardiothoracic radiologist. Final scores were determined by consensus. A severity score was assigned to each lobe based on the lung abnormalities detected being: 0 = no lung abnormalities, 1 = ground-glass opacities (GGO), 2 = GGO and consolidations, with GGO predominance, 3 = GGO and consolidations, with no predominance and 4 = GGO and consolidations, with consolidation predominance. According to the extension of the lung involvement (extension score) each of the five lung lobes was assessed for the percentage of the lobar involvement and classified as none (0% = score 0), minimal (1–25% = score 1), mild (26–50% = score 2), moderate (51–75% = score 3) or severe (76–100% = score 4). The total severity and extension score was reached by summing the five lobe scores in each patient (range from 0 to 20). Secondary outcomes were toxicity (CTCAE v5.0), days of hospitalization, changes in inflammatory blood parameters (ferritin, lymphocytes, C-reactive protein, d-dimer and LDH) and \(SatO_2/FiO_2\) index (SAFI), at day 0, +3 and +7. Discharge criteria included: resolution of fever for at least 48 h without use of antipyretic medication, maintaining \(O_2\) saturation >95% with low flow rate oxygen therapy with nasal cannula at ≤3 liters per minute, improvement of signs and symptoms requiring minimal supportive care (oral medication), ability to adhere to home isolation recommendations, and sufficient support at home.

Descriptive analyses were summarized as means with standard deviation (SD) and medians with interquartile ranges (IQR). A Wilcoxon sign rank test for paired data was used to assess the CT scores, SAFI index and blood work counts. Chi Square was used to assess for comparison of categorical variables. A two-tailed p-value of <0.05 was considered statistically significant. SPSS Statistics v.26 was used for all the analyses.

Results

Between April 2020 and February 2021 forty-one patients were included. Patient characteristics are summarized in Table 1. Median age was 75 (IQR 61–84). Eighteen patients (44%) previously received an anti-COVID treatment (Tocilizumab, Lopinavir/Ritonavir, Remdesivir). Thirty-nine (95%) patients were treated with steroids, 34 (83%) during LD-RT and 24 of them (58%) received dexamethasone ≥6 mg. Radiation treatment details are shown in Table 2. Dose received by 95% (D95%) of the PTV volume was 0.87 Gy, oesophagus and heart mean dose was 0.88 Gy and 0.89 Gy respectively. The median time to receive RT from the date of admission was 19 days (range 2–87). The median number of days in hospital after RT was 11 (range 4–78) and the median hospital admission time was 37 days (range 11–155). With a median follow-up of 60 days after LD-RT, 26 (63%) patients were discharged, 11 (27%) died because COVID respiratory failure and 4 (10%) died because another causes (2 due to bacterial sepsis and 2 due to ischemic colitis). Three patients died <72 h after LD-RT. Among the discharged patients, 19 (76%) required oxygen support at home with a mean of 2 litres per minute. 2 of them were already on O2 support prior to COVID infection.

Seventeen patients did not perform the second CT on day +3; 10 due to hemodynamic instability, 4 due to of logistic problems (as they came from another hospitals) and 3 had died. One week after LD-RT, 36 patients were alive, all but 3 of them (due to hemodynamic instability, 2 from ICU), performed the third CT scan on day +7. Patients who died < 72 h after LD-RT were excluded from the baseline score. The results of the extension score of the lesions in the lung parenchyma are shown in Table 3. The mean baseline extension score was 13.7 (SD ± 4.9) with a score of 12.2 (±5.2) at...
day 3, and 12.4 ± 4.7 at day 7. Although there were no significant changes between the baseline and the second CT (p = 0.3), there were statistically significant improvement between the baseline and the third CT (p = 0.002) and between the second CT and the third CT (p = 0.002) (Supplementary Material Table 1). One week after LD-RT, 17 patients (42%) experienced a radiological response in the extension score. Severity scores of the lung abnormalities are shown in Supplementary material Table 1. No significant differences were found comparing the scores between the baseline and second CT or third CT (p = 0.1); 22 patients (54%) showed no differences, 7 (17%) improved the score and 4 (10%) worsened it.

Baseline median SAFI was 147 (IQR 118–264), 230 (IQR 120–343) on day +3 and 293 (IQR 121–353) on day +7. At baseline 26 patients (63%) presented severe respiratory failure (SRF), 12 (30%) mild (MRF) and 3 (7%) normal SAFI index. On day +7, 14 (38%) SRF, 6 (16%) MRF and 17 (42%) recovered normal SAFI index. There was a significant SAFI improvement on day +3 and day +7 (p < 0.01) (Fig. 1). Sixteen patients (39%) experienced respiratory improvement within 72 h. One week after LD-RT, 17 patients (42%) recovered normal SAFI index. There was no significant correlation between SAFI and improvement of the extension score (p > 0.5).

No significant differences were found in ferritin, d-dimer and LDH comparing baseline with day +3 and day +7. Baseline median C-reactive protein (CRP) was 2.3 mg/dl (IQR 0.3–6), on day +3 was 1 mg/dl (IQR 0.5–7) and on day +7 was 0.6 mg/dl (IQR 0.3–4.3). A significant decrease was found in CRP on day +7 (p = 0.02) comparing with baseline. Baseline median lymphocytes count (LC) was 900 μL (IQR 400–1600), on day +3 was 700 μL (IQR 300–1200) and on day +7 was 650 μL (IQR 325–1175) (Supplementary material Fig. 1). There was a significant lymphocyte decrease on day +3 and day +7 comparing with baseline (p < 0.03).

Discussion

Recently, early results of two new antiviral drugs (Molnupiravir [19] and Paxlovid [20]) showed promising results in non-hospitalized patients with mild-to-moderate disease, reducing the risk of COVID-related hospitalization and death. These two antivirals could be game-changers, especially for patients with early-stage infection who are at high risk of severe disease. By stopping the virus from growing in the body, the drugs can prevent the inflammation that causes severe COVID-19. However, once the inflammation is established, the antivirals have not demonstrated clinical benefit [21].

LD-RT was being considered in several trials as potential treatment of COVID-19 hospitalized patients with encouraging outcomes (Table 4).

Our respiratory results are in agreement with previous published data [22–24]. Ameri et al. [6] analyzed 9 patients treated with 0.5 or 1 Gy and found a SatO2 improvement in 64% of them 24 h after RT. In our cohort there was significant SAFI improvement on day +3 and day +7 (p < 0.01).

In the same line, Hess et al. [5], comparing 10 patients treated with 1.5 Gy LD-RT with 10 control patients blindly matched by age and comorbidity, concluded that patients treated with LD-RT showed a significant faster recovery to room air than controls (3 days vs 12 days respectively, p = 0.05). Also, LD-RT cohort trended toward superior rates of delirium (p < 0.01), rate of intubation (10% vs 40%) and median time to hospital discharge (12 days vs 20 days). They found radiographic improvement in 90% of the patients treated with LD-RT versus 57% in the control group (p = 0.12) by day 21. We found a significant improvement one week after LD-RT in extension score, although comparing to Hess only 17 patients (42%) improved the score. The different outcome could be due to our sooner evaluation (one week versus 21 days).

Table 3

| Patients | 1st CT | 2nd CT | 3rd CT |
|----------|-------|-------|-------|
| 1st CT   | 18    | 18    | 17    |
| 2nd CT   | 18    | 18    | 17    |
| 3rd CT   | 17    | 17    | 17    |

1 Died before 2nd CT.
2 Died before 3rd CT.
and the different radiological score used. They subjectively assessed radiological tests and categorized them as improved, stable or worse and an acute respiratory distress syndrome scoring scale. In our study, we used specific scores for the assessment of COVID-19 pneumonia. Chung et al. [15] characterized the most common radiological findings and proposed a score according to the involvement. Li et al. [16], using the same score, found a high interobserver consistency and a high diagnostic ability relation. The severity score was based on the scoring system of Borghesi et al. [17] taking into account the stages of COVID-19 evolution and higher rate of comorbidities in the LD-RT group. Within our cohort, 7 patients (17%) were at ICU, 3 died and 4 were discharged.

Based on the encouraging results, large, randomized controlled trials could be the target population for future studies.

With a median follow-up of 60 days, 11 (27%) patients died because of COVID respiratory failure, 4 (10%) died because of other causes and 26 (63%) were discharged with similar median time to hospital discharge to that previously reported [5, 10].

One of the main concerns of using radiation is the risk of secondary tumors. Several studies tried to estimate the risk of carcinogenesis. Garcia-Hernandez et al. [27] reported a lifetime attributable risk of cancer (LAR) <1% for patients >60 years-old receiving 0.5 Gy. Similarly, Arruda et al. [28] using 1 Gy in the same cohort reported a LAR of 1.4% for females and 0.6% for males, as well as a cardiovascular risk of death <2%. Although cardiovascular estimations were comparable across the literature, some authors [29, 30] estimated an increased risk of lung cancer of up to 4% for 1 Gy. Shuryak et al. [24] added relevant risk factors such as smoking to the equation and found a LAR of lung cancer ranging from <1% to 4% depending on age, sex and baseline risk factors.

Limitations of this study included the small sample size, short follow-up and the absence of randomization with a control group which makes difficult to achieve robust conclusions. However, based on the results of the present study, patients >50 years-old, with oxygen requirement and inflammatory pattern on imaging tests could be the target population for future studies.

LD-RT is a well-tolerated treatment that is worth exploring. Based on the encouraging results, large, randomized controlled trials are needed to establish the clinical efficacy of LD-RT.
