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Original Article

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 $SatO_2/FiO_2$ 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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Since 2019 the world has been facing COVID-19 pandemic. Until now, over 173.6 million cases have been reported, with approximately 3.7 million deaths according to the World Health Organization [1]. Spain was one of the European countries most severely affected by the COVID-19 reaching more than 3.5 million infected and 80 thousand deaths [2]. Although most part of the patients present a mild disease, around 5% will develop severe acute respiratory syndrome. Initially, mortality in patients hospitalized for COVID-19 ranged from 4% to 54%, depending on risk factors such as age [3,4]. Many treatment options were explored in this setting with limited impact [5]; indeed, dexamethasone was the only treatment shown to significantly decrease 28-day mortality (22.9% vs 25.7% in the control group) [6].

Low-dose radiation therapy (LD-RT) has been used for decades to treat benign inflammatory disease because its known anti-inflammatory effect at doses of 0.5–1 Gy [7-9]. Recently, experi-

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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_{max}) < 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

Table 1
Patient characteristics.

Baseline characteristics	*N* (%)
Age	75 (61–84)
Sex	
Male	26 (63%)
Female	15 (37%)
Comorbilities	
HBP	20 (50%)
DM	17 (41%)
Heart disease	8 (21%)
COPD	7 (17%)
Obesity	5 (12%)
OSA	3 (7%)
Cancer	3 (7%)
Hypothyroidism	3 (7%)
Coagulopathies	2 (5%)
Domiciliary O_2	4 (10%)
ICU	7 (17%)
AntiCOVID treatment	
HCQ	10 (24%)
L/R	3 (7%)
RDM	4 (10%)
TZM	11 (27%)
Esteroids	39 (95%)

Abbreviations: AT = antithrombotic; ATB = antibiotic; COPD = chronic obstructive pulmonary disease; DM = diabetes; HBP = high blood pressure; HCQ = hydroxychloroquine; L/R = lopinavir/ritonavir; OSA = obstructive sleep apnea; RDM = remdesivir; TZM = tocilizumab.

Table 2
Radiation treatment details.

	Mean Gy (SD)
PTV D_{max}	1.12 (±3)
PTV D95%	0.87 (±3)
Lungs D_{max}	1.1 (±4)
Lungs D95%	0.91 (±3)
Mean lungs	1 (±2)
Mean oesophagus	0.88 (±8)
Mean heart	0.89 (±4)

PTV = Planning target volume; D_{max} = Maximal dose; D95% = Dose received by the 95% of the volume.

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).

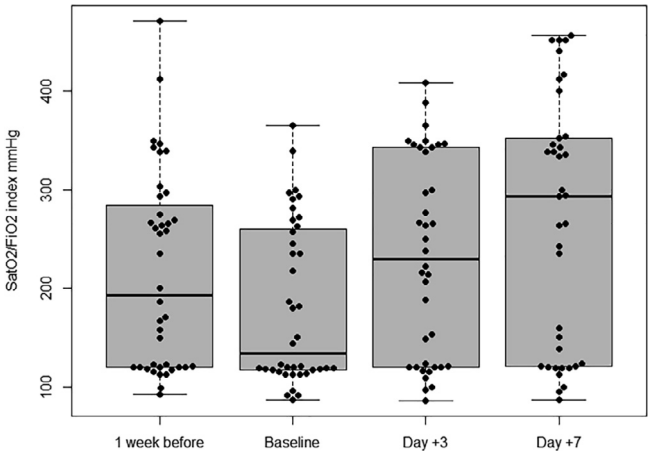

Fig. 1. $SatO_2/FiO_2$ index evolution.

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 $SatO_2$ 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
Extension score of lung abnormalities.

	Patients																					
	1*	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18†**	**19†**	**20**	**21**	**22***
1st CT	19	20	16	13	17	16	11	14	20	18	17	14	6	20	10	14	2	19	19	17	15	19
2nd CT	19	20	16	12	17	16	11	14			17		4				3			17	13	
3rd CT		15	14	11	16	16	6	11	20	18	17	14	3	20	7	12	1				12	
		23	**24**	**25**	**26†**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	Mean ± SD	
1st CT		18	10	1	14	12	5	14	19	12	12	12	12	8	10	20	20	12	13	12	13.7 ± 4.9	
2nd CT		18		1		12	5	14		8		12	12	8	10				15		12.2 ± 5.2	
3rd CT		17	9			12	5	12		8	12	12	12	8	10	18	19	16	14	12	12.4 ± 4.7	

†Died before 2nd CT.
*Died before 3rd CT.

Table 4
Summary of previous data.

Studies	Design	Inclusion criteria	Dose (Gy)	Sample size	Median age	Primary endpoint	Key results
Ameri el at. [13]	Phase II No randomized	>60 yo, SpO_2 <93% or RR >30/min	0.5–1	10	75	SpO_2 improvement	90% improved SpO2. 5 patients D/C, 4 died.
Hess et al. [12]	Phase I/II Matched controls	O_2 requirement, Rx involvement	1.5	20	78	Time to clinical improvement	12 vs 3 days for RT (p = 0.05). Improved delirium, biomarkers and trend Rx. 28d OS 90%.
Arenas et al. [22]	Phase I/II Multicentric Control group	Moderate–severe, <8 days of symptoms, not candidates for ICU	0.5–1	36	84	Improvement in SpO_2/FiO_2	SpO_2/FiO_2 at 24 h improved in 50% patients. 64% survived, 22% died from Covid.
Ganesan et al. [23]	Phase I/II Randomized	>40 yo, <10 days of symptoms, RR >24/min, SpO_2 <94% and SpO_2/FiO_2 ratio >89 and <357	0.5	25	57	Improvement in SpO_2/FiO_2	SpO_2/FiO_2 improved at 48 h, 3 d and 7 d (p = 0.025). Rx improvement.
Sharma et al. [24]	Phase II No randomized	Moderate to severe illness, RR >24/min and/ or SpO_2 <94%	0.7	10	51	Clinical recovery	Clinical recovery ranging from 3 to 7 days. 9 patients survived and 1 died.
Papachristofilou et al. [26]	Randomized Double-blind	ICU, Male>40yo, Female >50yo	1	22	75	Ventilator-free days at day 15	No differences VFDs. 28 d OS 63.6%.
This study	Phase I/II No randomized	>50 yo, O_2 requirement, Rx involvement	1	41	75	Radiological response	Extension score improved at 7d (p = 0.002). SpO2/FiO2 improved at 3d and 7d (p < 0.01). 63% patients D/C and 27% died from Covid.

yo = years-old; RR = respiratory rate; Rx = radiological; ICU = intensive care unit; D/C = discharged.

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. [18] taking into account the stages of COVID-19 evolution on CT proposed by Pan et al. [17].

Arenas et al. [9] evaluated 36 patients treated with 0.5 Gy classifying them in three groups: survivors (group A), deaths from COVID-19 (group B) and deaths from other causes (group C). They found an improvement in the respiratory parameters in groups A and C, and in the percentage of lung involvement in the CT scan at 1 week after LD-RT in group A. They reported a decrease in inflammatory parameters, especially CRP which decreased in all groups. We found a significant decrease in CRP one week after LD-RT and also in LC. The virus itself as well as dexamethasone could affect LC [25], in addition 28 patients (68%) in our cohort already presented at baseline any grade of lymphopenia. Ganesa et al. [10] also found significant reduction in LC at day 7 after LD-RT that recovers at day 14. Similarly, Papachristofilou et al. [26] randomized 22 ventilated patients from ICU to receive 1 Gy whole-lung RT or sham-RT and found relative reductions in LC more pronounced after LD-RT in patients with baseline lymphopenia. The results of this trial showed a lack of efficacy of LD-RT in critically ill COVID-19 patients; however, the authors acknowledged that the small sample size may make it difficult to find differences between groups. Also, although the baseline characteristics were similar between both groups, there was a higher proportion of patients managed with endotracheal intubation 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.

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.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.03.015.

References

[1] https://bestpractice.bmj.com/topics/en-gb/3000201/epidemiology.
[2] https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases.
[3] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.
[4] Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, Lumbreras-Bermejo C, Ramos-Rincón JM, Roy-Vallejo E, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry. Rev Clin Española (English Edition) 2020;220:480–94. https://doi.org/10.1016/j.rce.2020.07.003. Epub 2020 Jul 19. PMID: 32762922; PMCID: PMC7480740.
[5] Tarighi P, Eftekhari S, Chizari M, Sabernavaei M, Jafari D, Mirzabeigi P. A review of potential suggested drugs for coronavirus disease (COVID-19) treatment. Eur J Pharmacol 2021;895. https://doi.org/10.1016/j.ejphar.2021.173890.
[6] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693–704. https://doi.org/10.1056/NEJMoa2021436.
[7] Powell EV. Radiation therapy of lobar pneumonia. Texas State J Med 1936;32:237–40.
[8] Oppenheimer A. Roentgen therapy of "virus" pneumonia. Am J Roentgenol Rad Ther 1943;49:635–8.
[9] Quimby AJ, Quimby WA. Unresolved pneumonia: Successful treatment by roentgen ray. New York Med J 1916;103:681–3.
[10] Meziani L, Robert C, Classe M, et al. Low doses of radiation increase the immunosuppressive profile of lung macrophages during viral infection and pneumonia. bioRxiv 2020:2020.05.11.077651.
[11] Jackson MR, Stevenson K, Chahal SK, Curley E, Finney GE, Gutierrez-Quintana R, et al. Low-dose lung radiation therapy for COVID-19 lung disease: A preclinical efficacy study in a bleomycin model of pneumonitis. Int J Radiat Oncol Biol Phys 2022;112:197–211. https://doi.org/10.1016/j.ijrobp.2021.08.029.
[12] Hess CB, Nasti TH, Dhere VR, Kleber TJ, Switchenko JM, Buchwald ZS, et al. Immunomodulatory low-dose whole-lung radiation for patients with coronavirus disease 2019-related pneumonia. Int J Rad Oncol Biol Phys 2021;109:867–79. https://doi.org/10.1016/j.ijrobp.2020.12.011.
[13] Ameri A, Ameri P, Rahnama N, et al. Low-dose whole-lung irradiation for COVID-19 pneumonia: what is the optimal dose? Final results of a pilot study. Int J Rad Oncol Biol Phys 2020;108:1134–9. https://doi.org/10.20944/preprints202009.0229.v1.
[14] Sanmamed N, Alcantara P, Cerezo E, et al. Low dose radiotherapy in the management of covid19 pneumonia (LOWRAD-Cov19). Preliminary report. Int J Rad Oncol Biol Phys 2020;109(4):880–5. https://doi.org/10.1016/j.ijrobp.2020.11.049.
[15] Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV) Radiology, 2020;295: 202-7.
[16] Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol 2020;30:4407–16. https://doi.org/10.1007/s00330-020-06817-6.
[17] Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID19) pneumonia. Radiology 2020;295:715–21. https://doi.org/10.1148/radiol.2020200370.
[18] Borghesi A, Maroldi R. COVID-19 outbreak in Italy: experimental chest X-ray scoring system for quantifying and monitoring disease progression. Radiol Med 2020;125:509–13. https://doi.org/10.1007/s11547-020-01200-3.
[19] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. N Engl J Med 2022;386:509–20. https://doi.org/10.1056/NEJMoa2116044.
[20] Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. BMJ 2021;375:. https://doi.org/10.1136/bmj.n2713n2713.
[21] Arribas JR, Bhagani S, Lobo SM, Khaertynova I, Mateu L, Fishchuk R, et al. Randomized trial of molnupiravir or placebo in patients hospitalized with covid-19. NEJM Evid 2022;1. https://doi.org/10.1056/EVIDoa2100044.
[22] Arenas M, Algara M, De Febrer G, Rubio C, Sanz X, de la Casa MA, et al. Could pulmonary low-dose radiation therapy be an alternative treatment for patients with COVID-19 pneumonia? Preliminary results of a multicenter SEOR-GICOR nonrandomized prospective trial (IPACOVID trial). Strahlenther Onkol 2021;197:1010–20.
[23] Ganesan G, Ponniah S, Sundaram V, et al. Whole lung irradiation as a novel treatment for COVID-19: Interim results of an ongoing phase 2 trial in India. Radiother Oncol 2021;163:83–90.
[24] Sharma DN, Guleria R, Wig N, et al., Low dose radiation therapy for covid-19 pneumonia: a pilot study. medRxiv. 2020.
[25] Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): Systematic review and meta-analysis. J Intensive Care 2020;8:1–10.
[26] Papachristofilou A, Finazzi T, Blum A, Zehnder T, Zellweger N, Lustenberger J, et al. Low-dose radiation therapy for severe COVID-19 pneumonia: a randomized double-blind study. Int J Radiat Oncol Biol Phys 2021;110:1274–82. https://doi.org/10.1016/j.ijrobp.2021.02.054.
[27] García-Hernández T, Romero-Expósito M, Sánchez-Nieto B. Low dose radiation therapy for COVID-19: Effective dose and estimation of cancer risk. Radiother Oncol 2020;1:289–95.
[28] Arruda GV, Weber RRDS, Bruno AC, et al. The risk of induced cancer and ischemic heart disease following low dose lung irradiation for COVID-19: estimation based on a virtual case. Int J Rad Biol 2021;97:120–5. https://doi.org/10.1080/09553002.2021.
[29] Kirsch DG, Diehn M, Cucinotta FA, et al. Lack of supporting data make the risks of a clinical trial of radiation therapy as a treatment for COVID-19 pneumonia unacceptable. Radiother Oncol 2020;147:217–20.
[30] Shuryak I, Kachnic LA, Brenner DJ. Lung cancer and heart disease risks associated with low-dose pulmonary radiotherapy to COVID-19 patients with different background risks S0360-3016(21)00379-5. Int J Radiat Oncol Biol Phys 2021. https://doi.org/10.1016/j.ijrobp.2021.04.018.