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Low-dose Lung Radiotherapy for COVID-19-related Pneumonia: Preliminary Results of the Italian Mono-institutional COLOR-19 Trial

STEFANO MARIA MAGRINI[1], DAVIDE TOMASINI[1], EMANUELE FOCÀ[2], EMIRENA MICHELA GARRAFA[3], NAVDEEP SINGH[1], ANDREA EMANUELE GUERINI[1], LUCA TRIGGIANI[1], ROBERTO BRESCIANI[4], DIANA GRECO[1], LUDOVICA PEGURRI[1], SALVATORE LA MATTINA[1], ELENA RANGHETTI[1], GIULIA VOLPI[1], ROBERTO MAROLDI[5], MICHELA BUGLIONE[1] and LUIGI SPIAZZI[6]

[1]Department of Radiation Oncology, University of Brescia and Spedali Civili Hospital, Brescia, Italy;
[2]University Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili, Brescia, Italy;
[3]Department of Molecular and Translational Medicine and Clinical Chemistry Laboratory ASST Spedali Civili, Brescia, Italy;
[4]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy;
[5]Radiology Department, University of Brescia and Spedali Civili Hospital, Brescia, Italy;
[6]Medical Physics Department, ASST Spedali Civili Hospital, Brescia, Italy

Abstract. *Aim: To evaluate the feasibility and tolerability of low-dose radiotherapy (LDRT) delivered to both lungs in the treatment of SARS-CoV-2-immune-mediated pneumonia in the COLOR-19 study (NCT0437747). Patients and Methods: From May 2020 to April 2021 at Brescia University Radiation Oncology Department, three patients with COVID-19-related pneumonia were treated with LDRT according to the COLOR-19 protocol. All patients were treated with a single fraction at the average prescription dose of 0.7 Gy to both lungs. Results: Three patients were enrolled (two males and one female, aged 61-81 years) and underwent LDRT. Despite LDRT being safely performed without significant side-effects, two patients died (one 81-year-old male due to septic shock secondary to Escherichia coli infection and one 79-year-old male, already in poor condition, due to worsening of COVID-19). The remaining female patient (61 years old) underwent LDRT for less severe COVID-19: her clinical condition and chest X-ray improved, and she was discharged home completely asymptomatic 27 days after hospital admission. Blood levels of C-reactive protein and ferritin generally decreased after LDRT. Conclusion: Early results of the COLOR-19 study demonstrate the feasibility of LDRT for therapy of COVID-19-related pneumonia; no conclusions on the efficacy have been reached due to poor accrual.*

Correspondence to: Andrea Emanuele Guerini, MD, Piazzale Spedali Civili, 1, 25123 Brescia, Italy. Tel: +39 0303995272, e-mail: a.e.guerini@gmail.com

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The Brescia District was one of the regions in Italy most severely affected by novel Coronavirus Disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). A multitude of clinical trials have evaluated the use of several drugs, notably for the treatment of severe presentations [reviewed in (3)]. However, most studies to date have not shown a clear benefit of any drug, or led to controversial results (4, 5) and currently only remdesivir, steroids and tocilizumab are approved for the treatment of hospitalized patients with severe COVID-19 (6-9). As one of the main pathogenetic mechanisms leading to severe COVID-19 is the uncontrolled release of inflammatory molecules (10), different drugs with anti-inflammatory action have been tested. However, most studies were inconclusive and some of these drugs are burdened by high price and limited availability [reviewed in (11)]. Since low-dose radiotherapy (LDRT) has been widely and effectively used for decades in the treatment of various inflammatory diseases (12), we developed a clinical protocol with the aim of assessing its effect in the treatment of severe

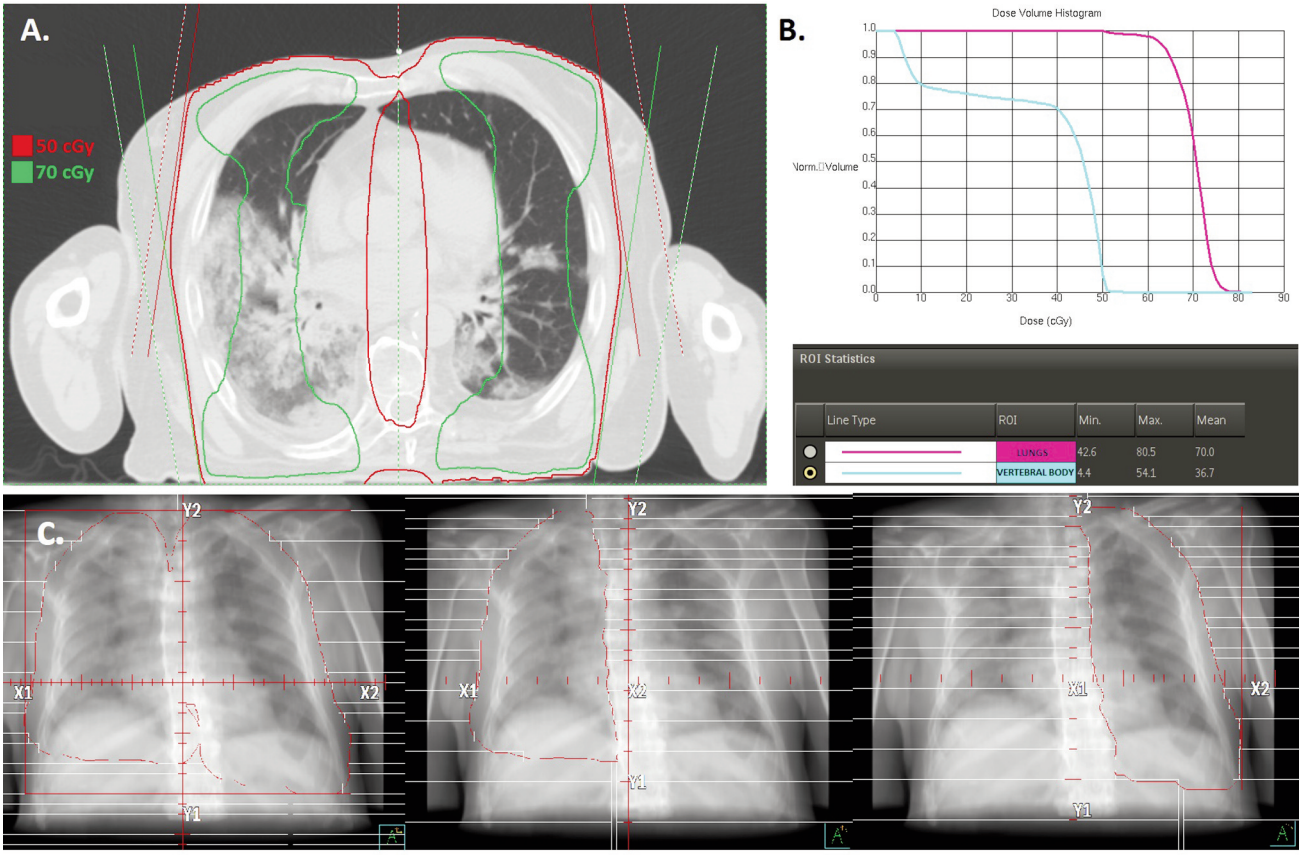

Figure 1. *A: Dose distribution and radiation fields of planning computed tomography -scan of patient 2, highlighting the sparing of the vertebral body. B: Dose-volume histogram for the same patient. C: Digitally reconstructed radiographs of the antero-posterior postero-anterior opposing fields, with the principal antero-posterior field conformed with multileaf-collimator to the whole lungs plus 2 cm and two beamlets (field-in-field technique) to treat each single lung minus vertebral bodies.*

forms of COVID-19 through the use of modern techniques. In this article, we report the preliminary results of the first enrolled patients

Patients and Methods

A pilot study COLOR-19 (COVID-19 Pneumonitis Low Dose Lung Radiotherapy; NCT0437747) started recruiting in May 2020. This study was approved by Spedali Civili of Brescia Ethic Board (approval number NP4097). The study was conducted in agreement with the Declaration of Helsinki and all patients provided written informed consent before enrollment and consent for publication of their data.

Three patients were treated with LDRT to both lungs. Patients underwent a single session of LDRT at the average prescription dose of 0.7 Gy, as per protocol. Dose constraints included a maximum dose of 0.55 Gy to vertebral bodies and 0.9 Gy to both lungs.

The irradiation was planned using the treatment planning system and performed by means of antero-posterior (AP) postero-anterior (PA) opposing fields with beamlets: the principal AP field was conformed with multileaf-collimator to the whole lungs plus 2 cm, then, with a field-in-field technique, we defined two beamlets to treat each individual lung minus vertebral body and sparing the contralateral lung. PA fields were specular (a fourth beamlet was added, if necessary, to decrease the dose to the most cranial vertebral bodies). Planning dose prescription was 70 cGy as the mean lung dose (Figure 1). We performed cone-beam computed tomography to verify the patient set-up. The overall required time for plan simulation and delivery was less than 30 minutes. All the enrolled patients required supplemental oxygen, which was safely continued during radiotherapy using portable oxygen sources or the medical gas supply available.

Inclusion criteria were: age ≥50 years; confirmed diagnosis of SARS-CoV-2 infection by polymerase chain reaction (PCR); Brescia Covid Respiratory Scale score 2-3; radiological findings of SARS-CoV2-induced pneumonia [evaluated by Brixia chest X-ray score (BS)]; at least three of the following laboratory criteria (C-reactive protein >5 times the maximum limit of normal, lactate dehydrogenase >2 times the maximum limit of the normal value, D-dimer >3 times the maximum limit of normal, aspartate aminotransferase >2 times the maximum limit of normal, total lymphocytes <1,000/ml, ferritin >500 ng/ml). Exclusion criteria were: age <50 years; active autoimmune disease; positive pregnancy test.

Table I. *Clinical features, comorbidities, and ongoing chronic treatments at COVID-19 diagnosis.*

Patient no., sex	Age, years	Comorbidities	Chronic therapy before COVID-19	Symptoms at diagnosis
1, Male	81	Hypertension, dyslipidemia, coronaropathy treated with PTCA, AAA treated with EVAR	Hydrochlorothiazide, clopidogrel, acetylsalicylic acid, rosuvastatin, ezetimibe, allopurinol, carvedilol, omeprazole	Fever, dyspnea
2, Male	79	Esophageal cT2N1M0 SCC, hypertension, diabetes mellitus complicated with retinopathy, prostatic adenocarcinoma (radical radiotherapy in 2009)	Gliclazide, omeprazole, bisoprolol, edoxaban	Asymptomatic
3, Female	61	cT2N0M0 SCC of the vulva	Oxycodone/naloxone	Asymptomatic

AAA: Abdominal aortic aneurysm; EVAR: endovascular aneurysm repair; PTCA: percutaneous transluminal coronary angioplasty; SCC: squamous cell carcinoma.

Brescia Covid Respiratory Scale (13) and BS (14) are scales developed during the first COVID-19 outbreak to classify clinical and radiological severity of COVID-19 easily. The primary outcome was the evaluation of the feasibility of LDRT with the purpose of a subsequent phase II study. Secondary outcomes were: modification of the chest X-ray according to BS at days 3, 6 and 10 after LDRT; evaluation of the safety and tolerability of LDRT according to Common Terminology Criteria for Adverse Events 5.0 (15).

Descriptive statistics were used to summarize patient's features. All statistical calculations were performed using SPSS Software version 25.0 (IBM, Armonk, NY, USA).

Results

Patients' characteristics are summarized in Table I, main parameters regarding COVID-19 evolution are given in Table II and trends of biochemical blood tests are reported in Table III.

Patient 1 was an 81-year-old man with multiple comorbidities (hypertension, dyslipidemia, coronaropathy treated with percutaneous transluminal coronary angioplasty, abdominal aorta aneurysm treated with endovascular repair) who tested positive by PCR for SARSCov-2 on October 19, 2020, through a naso-pharyngeal swab (NPS) performed for fever and dyspnea. He presented for worsening dyspnea at the Emergency Room of our Hospital on October 21st. Chest X-ray resulted in a BS of 14 and he was thus admitted to a dedicated COVID-19 ward. He started treatment with remdesivir with an initial improvement of chest X-ray (BS 5 on October 27th) but his clinical condition worsened, requiring non-invasive ventilation with continuous positive airway pressure. He started oral dexamethasone at 20 mg/day, enoxaparin 6000 UI/day and intravenous morphine with transitory benefit, but then his radiological (BS 10 on November 2nd) and general condition further deteriorated. He was thus enrolled to undergo whole-lung LDRT, which was performed on November 3rd. Treatment was well tolerated and at follow-up 3 days after LDRT, chest X-ray improved (BS 8) and ferritin and PCR load were slightly reduced. Nonetheless, on the same day, the patient developed septic shock due to systemic *Escherichia coli* infection, treated with intravenous antibiotics. Computed tomography excluded pulmonary embolism. At 6 days post LDRT, inflammatory indices further declined and SpO_2 was 96% despite a reduction of continuous positive airway pressure at 2 sessions/day alternated with a Venturi mask (10 l/min 50%). Unfortunately, the patient developed right heart failure and, despite hemodynamic support, his condition precipitated and he died on November 19th.

Patient 2 was a 79-year-old male with several comorbidities (hypertension, diabetes mellitus complicated with retinopathy, prostatic adenocarcinoma treated with radical radiotherapy in 2008) evaluated for esophageal cT2N1M0 squamous carcinoma of the middle third of the esophagus and in already poor general condition (Karnofsky score 60%) who was diagnosed with SARS-Cov-2 infection at a screening NPS on March 12th, 2021, while undergoing radical radiotherapy as an inpatient in our ward. Treatment was thus halted after 15 fractions of 2.3 Gy but 2 days later he manifested mild fever and dyspnea and his condition gradually worsened, requiring supplemental oxygen (Venturi mask 6 l/min, SpO_2 99%) despite administration of 6 mg/day dexamethasone. He also developed a urinary infection, treated with meropenem and vancomycin. On March 22nd, chest X-ray revealed a BS of 10, PCR was 196.7 mg/l and ferritin 5998 μg/l. He underwent whole-lung LDRT on March 23rd. However, notwithstanding a slight reduction of the PCR load, his clinical, respiratory and radiological (BS 12 on March 25th) condition declined, and he died on March 26th.

The third patient was a 61-year-old female in good general condition with a cT2N0M0 squamous carcinoma of the vulva and no other comorbidities. She started radical radiotherapy (prescribed dose 59.4 Gy/33 fractions) on February 25th with

Table II. *Main parameters regarding the clinical course of COVID-19 in the study patients.*

Patient		Symptoms	KPS	Oxygen supplementation	BS	CRP, mg/l	Ferritin, ng/ml	HGS	COVID-19 treatment	Complications	Treatment for complications
1	Diagnosis (19/10/2020)	Dyspnea, fever	70		14	253.8					
	Before RT (02/11/2020)	Dyspnea, fever	60	Continuous CPAP, SpO_2 100%	10	60	2,500	pO_2 83% pCO_2 33%			
	3 Days post RT (06/11/2020)	Improved dyspnea, fever	60	Mask 15 l/min with reservoir alternated with CPAP; SpO_2 94%	8	57.9	1,999		Oral dexamethasone at 20 mg/day, enoxaparin at 6,000 UI/day	Septic shock from Escherichia coli	Vancomycin, meropenem, noradrenaline, crystalloids and albumin
	6 Days post RT (09/11/2020)	Improved dyspnea, fever	60	Venturi 10 l/min 50%, CPAP twice daily;	8	48.4	1,540	pO_2 92% pCO_2 31%			
	10 Days post RT (13/11/2020)	Deterioration of general conditions, confusion	40	SpO_2 96%		17	1,381				
	Last follow-up (19/11/2020)	Death due to septic shock									
2	Diagnosis (12/03/21)	Asymptomatic	60								
	Before RT (22/03/21)	Dyspnea, fever	50	Mask 6 l/min, SpO_2 99%	10	196.7	5,998		Oral dexamethasone at 6 mg/day	Urinary tract infection	Vancomycin, meropenem
	3 Days post RT (25/03/21)	Dyspnea, fever, confusion		Mask 15 l/min with reservoir; SpO_2 90%	12	161.3		PO_2 55.7% pCO_2 31%	Oral dexamethasone at 20 mg/day, enoxaparin at 6,000 UI/day	Urinary tract infection, atrial flutter	
	Last follow-up (26/03/21)	Death due to deterioration of general condition									
3	Diagnosis (19/03/2021)	Asymptomatic	90								
	Before RT (29/03/2021)	Mild dyspnea, fever	80	Nasal cannula 4 l/min, SpO_2 95%	7	44	1,059				
	3 Days post RT (02/04/2021)	Improved dyspnea, fever	80	Nasal cannula 2 l/min, SpO_2 97%	7		888		Oral dexamethasone at 6 mg/day, enoxaparin at 4,000 UI/day		
	6 Days post RT (06/04/2021)	Improved dyspnea	80	Nasal cannula 2 l/min, SpO_2 98%	7 (07/04/21)	5.1	575				
	10 Days post RT (09/04/2021)	Improved dyspnea	80	Nasal cannula 1 l/min, SpO_2 98%		1.6	524				
	Last follow-up (16/04/2021)	Asymptomatic Discharged home	90	Weaned from O_2 therapy on 12/04, SpO_2 97%	6 (15/04/21)	56.4			Enoxaparin at 4,000 UI/day		

BS: Brixia score for chest X-ray; CPAP: continuous positive airway pressure; CRP: C-reactive protein; HGS: hemo gas analysis; KPS: Karnofsky performance score; SpO_2: peripheral capillary oxygen saturation.

Table III. *Main parameters regarding biochemical trends of circulating molecules and radiological findings.*

Laboratory findings	Patient	At diagnosis	Day 0	Day 3	Day 6	Day 10
WBC, n/ml	1	NA	18,890	10,710	6,500	9,190
2	2,080	1,990	1,990	2,190	NA	
3	2,940	3,660	3,550	3,870	2,960	
Neutrophils, n/ml	1	NA	17,920	9,900	5,870	8,310
2	1,680	1,820	2,030	NA	NA	
3	2,390	3,280	3,160	3,330	1,820	
Lymphocytes, n/ml	1	NA	440	480	390	480
2	240	110	60	NA	NA	
3	240	160	160	180	280	
AST, mg/ml	1	NA	43	NA	NA	NA
2	NA	129	NA	NA	NA	
3	33	28	28	26	57	
LDH, mg/ml	1	NA	534	291	NA	463
2	235	359	NA	NA	NA	
3	336	444	359	361	205	
CRP, mg/ml	1	253.8	60	57.9	48.4	17
2	148	196.7	161.3	NA	NA	
3	13.5	44	63	5.1	1.6	
Ferritin, ng/ml	1	NA	2,500	1,999	1,540	1,381
2	NA	5,998	NA	NA	NA	
3	NA	1,059	888	575	524	
D-Dimers, ng/ml	1	NA	985	NA	NA	NA
2	NA	1,048	NA	NA	NA	
3	618	701	774	NA	625	
Brixia score	1	14	10	8	10	–
2	NA	10	12	NA	–	
3	7	7	7	7	–	

AST: Aspartate aminotransferase; CRP: C-reactive protein; LDH: lactate dehydrogenase; NA: not assessable; WBC: white blood cell count.

concomitant 5-fluorouracil and mitomycin therapy (one cycle started on March 1st). On March 19th, she tested positive for SARS-Cov-2 at a screening NPS and 3 days later, she developed fever and mild dyspnea, chest X-ray showed BS 1. In the following days, she required supplemental oxygen and treatment with dexamethasone (6 mg/day) and enoxaparin (4,000 UI/day) was started. On March 29th, chest X-ray worsened to BS 7, and she was thus enrolled for whole-lung LDRT, performed on March 30th. The treatment was well tolerated and, despite no change in her chest X-ray, her respiratory function improved; D-dimers increased to over 35,000 μg/l, but embolic processes were ruled out. Supplemental oxygen was gradually reduced, and PCR load also decreased, but the chest X-ray remained unchanged; D-dimers sharply diminished. On April 9th, PCR was 1.6 mg/l and SpO_2 of 98% was achieved with nasal cannula at 1 l/min; she was finally weaned from oxygen on April 12th. April 14th, she completed radiotherapy at the prescribed dose; on the same day, the chest X-ray had improved to BS 6. She was discharged from hospital on April 16th with no respiratory symptom; she continued isolation at home until she received a negative NPS on April 23rd and she is still asymptomatic

Discussion

Although our results support the feasibility of LDRT for COVID-19-related pneumonia, several factors limit the reliability and the reproducibility of the data: the limited sample size, the extreme variability of patients' baseline characteristics and COVID-19 severity, and timing from the onset of symptoms to the administration of LDRT. Moreover, the study protocol did not exclude pharmacological treatment, hence patients were referred to our Department after the failure of previous medical treatments. Nevertheless, the results of this small trial may provide some interesting data in this field and be useful for future studies including LDRT. Indeed, proper patient selection and timing of LDRT emerged as the main critical aspects in exploiting the anti-inflammatory efficacy of LDRT. Patient 1 received a partial benefit from LDRT, with an initial reduction of chest X-ray BS, inflammatory indices, and necessity for respiratory support; unfortunately, he died due to septic shock from *Escherichia coli* infection. The poor general condition and the severity of pneumonitis were likely the reasons for LDRT failure in patient 2. Patient 3 was probably an ideal candidate for LDRT: hyper-inflammation was

properly intercepted at the right time; the severity of the COVID19-induced pneumonia was acceptable (as demonstrated by the initial low BS and the minimum need for supplemental oxygen). No patients were transferred to the Intensive Care Unit and patient 3 was discharged after 27 days of hospitalization. Several aspects remain to be clarified regarding the use of LDRT for COVID-19-related pneumonia, including a) Ideal timing, likely before hyper-inflammation peak as suggested by our experience and the available literature (16-19); b) optimal radiotherapy technique; and c) dose and fractionation of LDRT, as multiple schedules have been used (including 2-fraction regimens and doses up to 1.5 Gy) (16-19). Although a small-cohort randomized double-blind study reported no clinical benefit of LDRT for COVID-19 (20), enrolled patients were all on mechanical ventilation (thus possibly beyond the 'window of opportunity') and the adopted technique implied a large dosimetric inhomogeneity throughout the target volume (0.5 to 1 Gy).

In conclusion, although the issue is controversial (20, 21), our results support the feasibility of LDRT for treatment of COVID-19-related pneumonia. Accurate planning and delivery are feasible in a reasonable time. No conclusions regarding effectiveness could be drawn, due to the small sample size. Larger trials are required to demonstrate clinical benefit and optimal timing, technique, and schedule of LDRT.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

Authors' Contributions

Conceptualization: SMM, DT, EF, EMF, RM, MB and LS. Formal analysis: SMM, DT, NS, AEG, LT, RB, DG, LP, SLM, ER, GV, RM, MB and LS. Methodology: SMM, DT, NS, AEG, LT, RB, DG, LP, SLM, ER, GV, RM, MB and LS. Investigation: SMM, DT, EF, EMF, NS, AEG, LT, RB, DG, LP, SLM, ER, GV, RM, MB and LS Data curation: DT, EF, EMF, NS, AEG, LT, RB, DG, LP, SLM, ER and GV Supervision: SMM, DT, NS, AEG, LT, RB, RM, MB and LS. Writing – original draft: SMM, DT, NS, AEG, LT, RB, RM, MB, LS. Writing – review and editing: SMM, DT, EF, EMF, NS, AEG, LT, RB, DG, LP, SLM, ER, GV, RM, MB and LS.

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