Dose Estimates of an Early 20th Century Kilovoltage Radiotherapy Treatment for the Potential Application to Viral Pneumonia Using Modern X-Ray Equipment

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Abstract

Purpose: To simulate an early 20th century radiotherapy pneumonia treatment to evaluate the viability of using modern fluoroscopes to deliver a low-dose single-fraction treatment to the lungs and to compare calculated organ doses to current tolerance guidelines.

Materials and Methods: PENELOPE v.2008 was used to simulate a 1920s-40s radiotherapy treatment to both lungs of pneumonia patients using a modern beam quality. Organs-at-risk were: skin, breasts, esophagus, ribs, vertebrae, heart, thymus and spinal cord. A 100 kV_p beam with 3 mm Al HVL, 25 x 25 cm^2 posterior-anterior field and 50 cm source-to-surface distance were used. Simulations had a resolution of 0.4 x 0.4 x 0.06 cm^3 and a 6% uncertainty. 100% dose was normalized to the skin surface and results were displayed in axial, coronal and sagittal planes. Dose volume histograms were generated in MATLAB for further analysis. Prescriptions of 0.3, 0.5 and 1.0 Gy were applied to the 15% isodose line for organ dose comparison to modern tolerances.

Results: Right and left lung volumes were well-covered by the 15% isodose (95% and 97%, respectively). Mean doses were: lungs 28% (right) 29% (left), breasts 6% (right and left), skin 16%, esophagus 16%, ribs 66%, vertebrae 55%, heart 11%, thymus 5% and spinal cord 22%. For all prescriptions, absolute maximum skin doses were above the transient erythema threshold (2.0 Gy), while lungs were below pneumonitis (6.5 Gy) and fibrosis (30.0 Gy) thresholds. For 0.5 and 1.0 Gy prescriptions, maximum heart doses were above the 0.5 Gy ICRP-recommendation. Maximum doses to other organs were below modern dose thresholds.

Conclusion: All prescriptions normalized to the 15% isodose line would have resulted in lung doses without risk of complications. Skin and heart maximum doses could have reached detriment thresholds, particularly for the 1.0 Gy prescription. Equal-or-better treatments should be possible with a modern fluoroscope.

Keywords: radiotherapy, pneumonia, kilovoltage x-rays, low dose, fluoroscopes, c-arm

Introduction

In the early 20th century, viral and bacterial pneumonia patients were treated with radiotherapy to deliver lung doses of 0.3-1.0 Gy using 100-200 kV_p x-ray beams. This was a one-time treatment and signs of recovery appeared as early as 3-5 hours after irradiation. Radiotherapy treatments stopped in the 1940s with the advent of antibiotic- and steroid-therapies despite their high cure rate.[1] However, the potential to use radiotherapy for the treatment of viral pneumonia has been suggested in modern times and is an area of research for treating COVID-19 patients.[1-3] Modern fluoroscopes could deliver therapeutic radiation doses to the lungs using x-ray energies similar to those used historically, and they are more widely available than radiotherapy linear accelerators.

It is worth exploring the dosimetry that a historical pneumonia treatment could have achieved via computer simulations using a kV x-ray beam on an anthropomorphic phantom. Reproduction of a beam quality of the era would have required a detailed description of materials, dimensions and design of a 1920s-40s x-ray source, which is not readily available. Therefore, a modern x-ray tube with minor modifications was used, which can lead to an experimental verification with existing systems in the future. Prescription dose information can be extracted from published clinical and historical reports[1-6,9-12] and used in the simulations.

In this study, prescription doses of 0.3, 0.5 and 1.0 Gy were used for isodose normalization while dose distributions and maximum doses to critical organs were evaluated according to

modern dose tolerance guidelines. Results from this work and potential implementation using modern fluoroscopes are presented.

Materials and Methods

PENELOPE with its mathematical anthropomorphic phantom was used for Monte Carlo (MC) simulations.[7] The phantom was an adult female anatomy that included most organs (Fig. 1a-b) with published density information for each of them. Each lung was 24 cm superior-inferior, 12 cm left-right and 10 cm anterior-posterior. Organs-at-risk were: skin, breasts, ribs, esophagus, vertebrae, heart, thymus and spinal cord. Skin volume was limited to the thoracic region only.

SPEKTR 3.0[8] was used to generate a 100 kV_p x-ray beam spectrum from a tungsten target with an aluminum filter. Historically, a single- or three-phase generator[5] would have produced significant ripple and a lower effective energy than a modern beam; however, 100 kV_p is at the bottom of the cited energy range, so the effective energy should still be appropriate for the historical context. A report of that time recommends the use of a 3-mm Al filter for x-ray radiotherapy of the lungs,[9] which would result in a half-value layer (HVL) of approximately 3 mm Al, assuming an inherent tube filtration similar to modern tubes and tube ripple appropriate for a 3-phase generator[1]. Thus, a 3 mm Al HVL was selected for the simulated beam, which is a slightly softer spectrum than on modern units.[10]

[1] Calculated using IPEM 78 Spectrum Processor Version 3.0. The Institute of Physics and Engineering in Medicine. 2015

The simulated treatment consisted of a 25 x 25 cm^2 posterior-anterior (PA) field at 50 cm source-to-surface distance (SSD) (Fig. 1c). The field covered both lungs and could have been

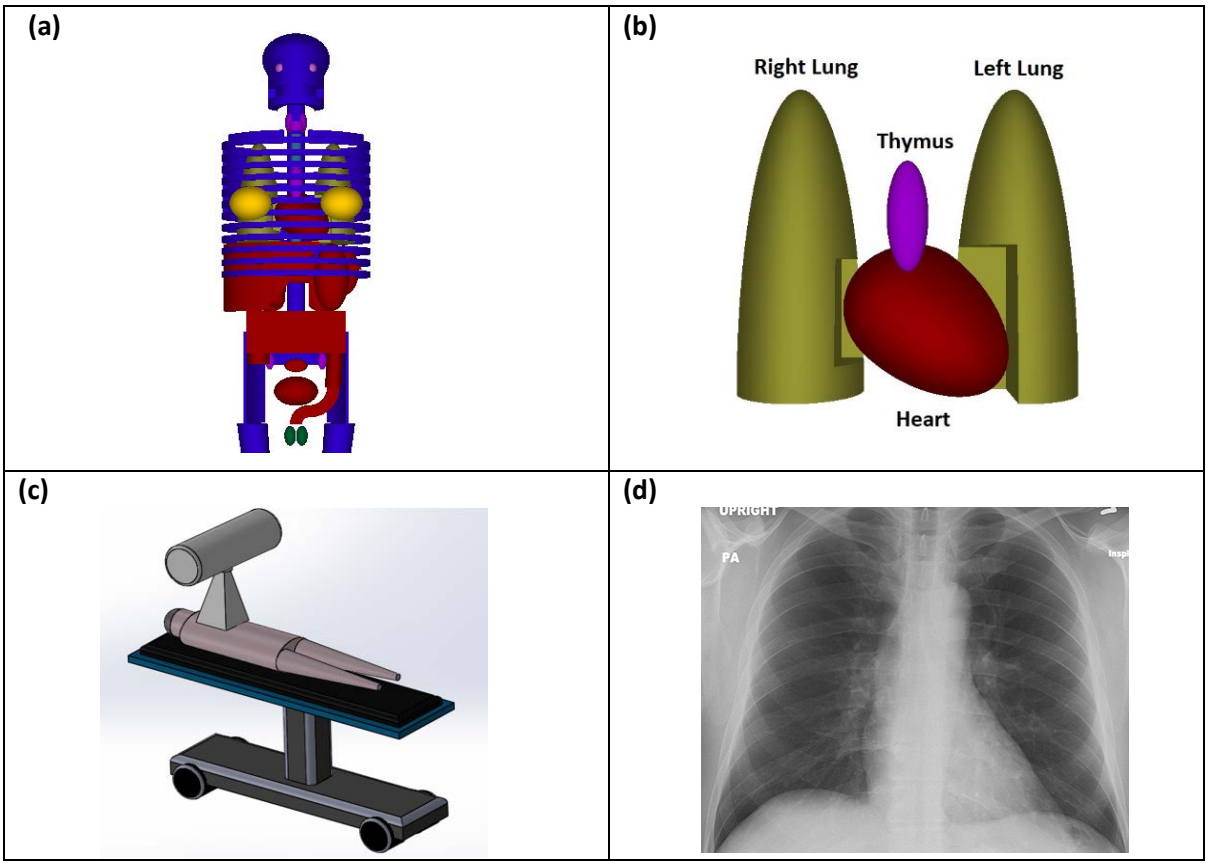

Figure 1. (a) PENELOPE's mathematical anthropomorphic phantom of a female anatomy. (b) Thoracic anatomy inside the phantom. (c) Posterior-anterior treatment field used in the simulations. (d) Posterior-anterior tuberculosis chest x-ray during the first world war.[11]

defined with an x-ray system of that time (Fig. 1d) which was used for radiography, fluoroscopy and radiotherapy procedures.[4-6,9,11,12]

The simulations had a spatial resolution of 0.4 x 0.4 x 0.06 cm^3 and an uncertainty of 6% for 2 x 10^9 histories. Cumulative dose volume histograms (DVHs) were generated in MATLAB (MathWorks, Natick, MA) and the MATLAB DVH code was validated using a known data set

prior to the actual data analysis. DVHs were generated for the left/right lungs, skin, left/right breasts, esophagus, ribs, vertebrae, heart, thymus and spinal cord.

The skin surface dose corresponded to 100% and was the reference dose calibration location. The 15% isodose was normalized to a 0.3, 0.5 and 1.0 Gy prescription dose to extract absolute dose information. Mean and maximum relative doses for each organ-at-risk were extracted from the DVHs, normalized to each prescription dose, and evaluated against the International Commission on Radiological Protection (ICRP) and other reports for organ dose tolerance assessment.[13-22]

Results

Figure 2a shows the percent depth dose (PDD) at the phantom's central sagittal plane. Peak doses at 0.5, 3.0, 5.5, and 19.5 cm depths corresponding to ribs or vertebrae regions resulted from photoelectric interactions. The most prominent peak was in the ribs at 0.5 cm depth with a 325% maximum point dose. The second-most prominent was in the vertebrae at 3 cm depth with 225% maximum dose. Conversely, soft tissue regions showed a smooth dose deposition reduction as a function of depth.

Figures 2b-2d show axial, coronal and sagittal isodoses. The 15% isodose provided coverage to both lungs with 95% and 97% of the right and left lung volumes covered as shown in the DVH (Fig 3a). The peak doses to the lungs were 72% (right) and 73% (left) of the maximum dose.

Table 1 shows mean and maximum absolute doses for the lungs, skin, breasts, esophagus, ribs, vertebrae, heart, thymus and spinal cord, after applying a 0.3, 0.5 and 1.0 Gy prescription dose

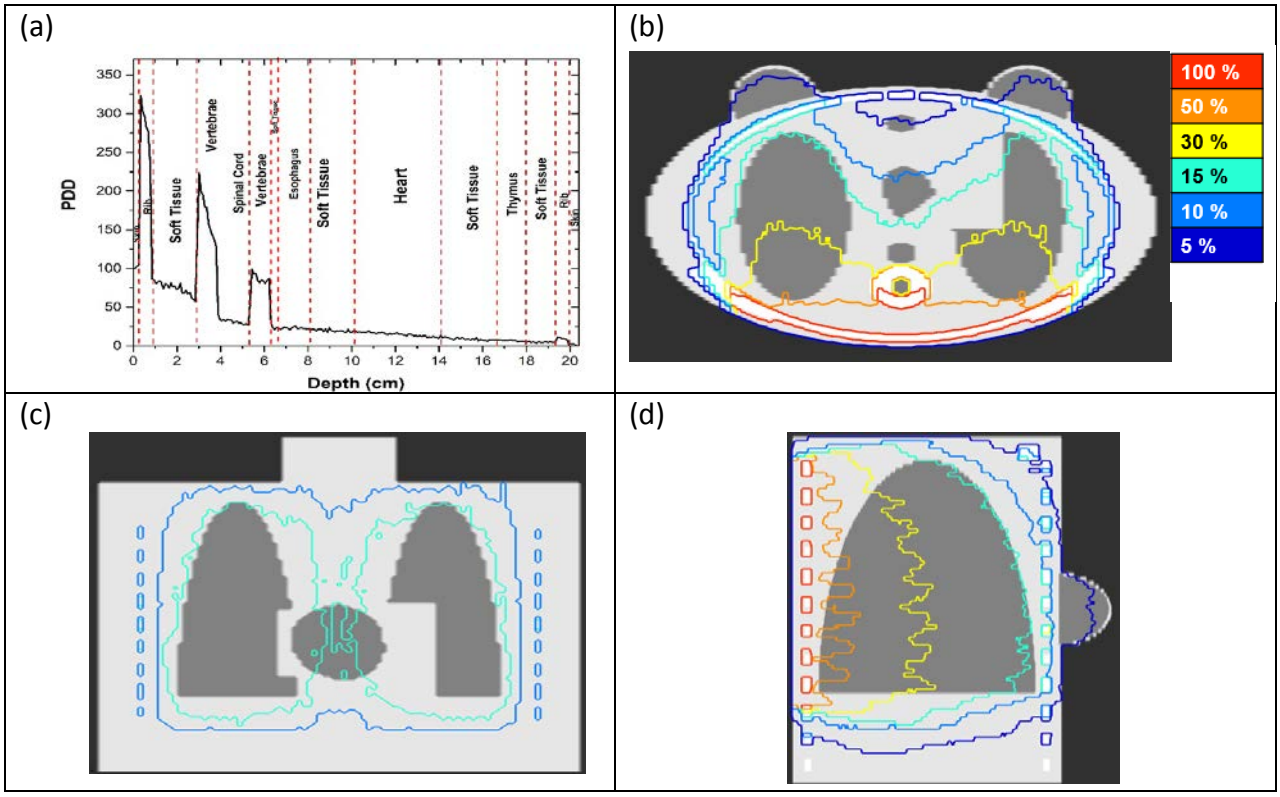

Figure 2. Percent depth dose with 100% at the skin surface (a) and dose distribution displayed in the axial (b), coronal (c) and sagittal (d) planes. The 15% isodose (cyan) distribution provided an effective dose coverage to both lungs.

normalization to the 15% isodose, as well as dose tolerances provided by ICRP and other reports. The maximum dose to the skin exceeded 2 Gy[13-15] (the transient erythema dose threshold) by 44%, 240%, and 480% for the 0.3, 0.5, and 1.0 Gy prescriptions, respectively. The heart maximum dose exceeded 0.5 Gy (the threshold for potential cardiovascular and blood circulatory effects) by 5%, 76%, and 352% for the 0.3, 0.5, and 1.0 Gy prescriptions, respectively.[13,15,16] The heart mean dose also exceeded this threshold by 42% for the 1.0 Gy prescription, while it remained below the threshold for the 0.3 Gy and 0.5 Gy prescriptions.

Maximum doses to the lungs did not pose any risk for pneumonitis (6.5 Gy threshold for acute exposure)[13,17] or fibrosis (30.0 Gy threshold)[17] for any prescription dose. The lung mean doses

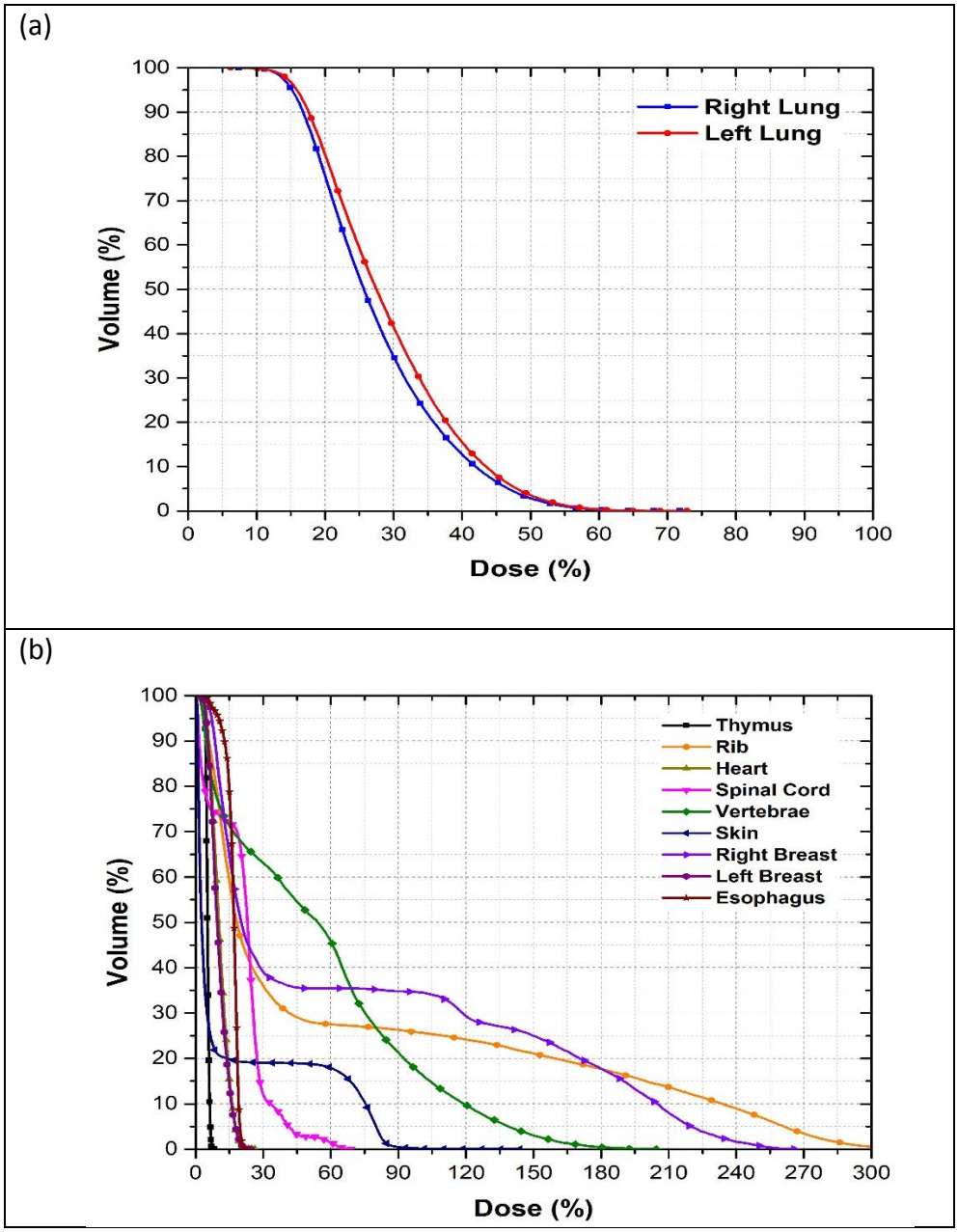

Figure 3. Cumulative dose volume histograms for the right/left lungs (a) and organs at risk (b).

129

130suggested a prescription dose normalization to the 20% instead of the 15% isodose could be used

131which would result in lower doses to critical organs. Mean and maximum doses to the breast were

132below the proposed 1.0 Gy dose threshold at which the risk for developing secondary cancers

133increases in women younger than 40 years.[18]

134

135**Table 1.** Mean and maximum relative and absolute doses are shown for prescription doses of 0.3, 0.5 and 1.0
136Gy normalized to the 15% isodose line and compared to modern dose tolerance data.

Organ	Relative Dose		0.3 Gy prescription		0.5 Gy prescription		1.0 Gy prescription		Modern Dose Tolerances (Gy)
	Mean (%)	Max (%)	Mean (Gy)	Max (Gy)	Mean (Gy)	Max (Gy)	Mean (Gy)	Max (Gy)	
Right Lung	27.6	71.8	0.55	1.44	0.92	2.40	1.84	4.79	6.5 [13] (pneumonitis) 30.0 [17] (fibrosis)
Left Lung	29.0	72.8	0.58	1.46	0.97	2.43	1.93	4.86	
Skin	16.3	144.0	0.33	2.88	0.54	4.80	1.09	9.60	2.0 [14] (transient erythema)
Right Breast	5.6	12.6	0.11	0.25	0.19	0.42	0.37	0.84	1.0 Gy < For < age 40 2.5 fold risk [18] For age 40 <, no excess risk [18]
Left Breast	6.3	12.4	0.13	0.25	0.21	0.41	0.42	0.83	
Ribs	66.4	324.0	1.33	6.48	2.21	10.80	4.43	21.60	< 30.0 Gy [21,22] single faction 22.0 Gy for < 1 cc
Vertebrae	54.8	204.5	1.10	4.09	1.83	6.82	3.65	13.64	12.4-14.0 [21,22] single fraction
Heart	10.6	26.3	0.21	0.53	0.35	0.88	0.71	1.76	0.5 [13,15] 3.0-4.0 [16]
Thymus	5.3	8.4	0.11	0.17	0.18	0.28	0.35	0.56	0.71 [20]
Spinal Cord	20.3	69.1	0.41	1.38	0.68	2.30	1.35	4.60	7.0 [21,22] single fraction
Esophagus	16.4	22.4	0.33	0.45	0.55	0.75	1.09	1.50	40.0-45.0 [19] (acute esophagitis) < 34.0 [22] (mean dose)

Ribs maximum doses (prescription dose) were 78% (0.3 Gy), 64% (0.5 Gy) and 28% (1.0 Gy) below the 30.0 Gy single-fraction dose threshold. Furthermore, the dose to 1 cm^3 of the ribs' volume, for all prescriptions, was below the 22.0 Gy single-fraction dose threshold.[21,22] The vertebrae maximum doses (prescription dose) were 67% (0.3 Gy) and 45% (0.5 Gy) below, but 11% (1.0 Gy) above the 12.4 Gy single-fraction dose threshold.[21,22] Ribs and vertebrae maximum doses for all prescriptions far exceeded the ICRP 118 recommended limit of 2.0 Gy dose per fraction but not the cumulative dose limit of 50.0 Gy.[13] Mean and maximum doses to other critical organs for all prescription doses were well within modern dose tolerances.

Discussion

Calabrese et al.,[1] were the first to suggest re-visiting the role of radiotherapy to treat pneumonia and now, this suggestion has a newfound relevance in light of the COVID-19 pandemic. Early animal experiments demonstrated that low radiation doses upregulated lymphocytosis and reduced inflammation.[1,2,27,28] Today, modern studies support these conclusions.[29,30] This investigative dosimetric analysis provides quantitative information on dose distributions and detriments to organs from such radiation treatments and suggests a potential treatment delivery with bedside c-arm fluoroscopes in an inpatient setting.

For a simple treatment setup consisting of a PA field, the 15% isodose provided effective coverage to the lungs with 95% and 97% of the right and left lung volumes covered. After applying a 0.3, 0.5 or 1.0 Gy prescription dose to the 15% isodose, the maximum dose to the lungs did not exceed modern thresholds for pneumonitis or fibrosis.[13,17] However, it could have

158 exacerbated pre-radiation fibrosis caused by the pneumonia and/or affected patients with
159 borderline interstitial fibrosis.

160 For the 0.3 and 0.5 Gy prescriptions, the resulting 2.0-5.0 Gy skin dose may produce signs of
161 transient erythema within two weeks after exposure, recoverable epilation within eight weeks,
162 and no observable effects after 40 weeks.[14] For skin doses of 5.0-10.0 Gy, expected from a 1.0
163 Gy prescription, transient erythema could manifest within two weeks, possible prolonged
164 erythema and permanent epilation within eight weeks, and at the upper end of the dose range,
165 dermal atrophy and induration after 40 weeks.[14] It is likely that for the 0.3 and 0.5 Gy
166 prescriptions, detrimental skin effects would not be permanent, but that may not be the case
167 for a 1.0 Gy dose.

168 The 0.5 and 1.0 Gy prescriptions had maximum doses to the heart that significantly exceeded
169 the 0.5 Gy dose threshold for possible cardiovascular and blood circulatory effects according to
170 the ICRP 118 report.[13] The ICRP 120 report[15] supports the 0.5 Gy threshold statement;
171 however, it adds that some uncertainty remains at this threshold. Other studies suggest that
172 the risk of radiation-related heart disease from a low dose radiotherapy can begin to manifest
173 at 3.0-4.0 Gy.[16] It is possible that a maximum heart dose of 0.9 Gy (0.5 Gy prescription) or 1.8
174 Gy (1.0 Gy prescription) could cause microvascular damage to the myocardium, however, the
175 risk for heart-related complications would be low. Furthermore, peak skin doses from modern
176 interventional cardiac procedures routinely exceed 2.0-3.0 Gy,[23] which implies that cardiac
177 doses over 0.5 Gy are frequent and not an impediment to treatment. The 0.3 Gy prescription
178 did not exceed this limit.

Maximum doses to the ribs and vertebrae for all prescriptions were below dose thresholds for a single fraction treatment.[21,22] However, they far exceeded (≥200%) the recommended ICRP 118 fractionated dose of 2.0 Gy.[13] Although the risk of radionecrosis, rib fracture, and/or muscoskelethal atrophy would be low, no additional treatments without risk of complications would be possible with this setup. Additional treatment fields, such as anterior-posterior (AP) or laterals, could reduce maximum doses to these structures, but not below 2.0 Gy at the higher prescribed doses.

Published reports indicate that women under the age of 40 could have a 2.5-fold greater risk of secondary cancers if exposed to a dose greater than 1.0 Gy, compared to no risk for older women 10 years after irradiation.[18] In this work, median doses to the breasts were below this level suggesting little-to-no detrimental effects. Maximum doses to the spinal cord, esophagus and thymus were within modern dose tolerances and did not pose risk of future detriment.[13,19-22]

This study indicates that a radiotherapy pneumonia treatment with a PA field and a 0.3 or 0.5 Gy prescription dose to both lungs would have a low probability of radiation-induced detriment to critical organs. However, a 1.0 Gy dose treatment might be problematic. Treatment setups employing more fields could result in a more homogeneous dose distribution to the lungs, and lower dose to critical organs; this is an area of future work.

Treatment setups with two or more fields and hardened beams are possible with modern fluoroscopes. Fixed interventional c-arms could be ideal due to their large, highly-filtered x-ray beams, higher x-ray tube heat capacities, and ease of positioning. Mobile c-arms could also be used for this purpose, albeit with longer treatment times but with the convenience of an in-situ

treatment delivery. Modern fluoroscopes do not have field sizes as large as those simulated, however, therapy covering the entire lung field is possible with multiple beam angles.

A modified fluoroscopy unit with a larger field size might be possible with manufacturer support . While such a system may not be legally used for imaging in the U.S., it could potentially be used as an investigational device under IRB approval. Perhaps another option could be the use of existing fluoroscopes on targeted treatments to affected areas identified on CT.[24]

The prospect of rapid, inexpensive, and non-invasive therapy to reduce or prevent ventilator requirements could be invaluable and even paradigm-changing for centers with limited ventilator supplies. Clinical trials to evaluate the efficacy of low-dose radiation with linear accelerators for COVID-19 patients are underway in India, Iran, Italy, Spain, and U.S. However, there are no trials exploring the use of a c-arm based delivery.

Low dose treatments (0.3-0.5 Gy) via mobile c-arm fluoroscope in-situ (e.g. at the patient bedside in intensive care units or emergency rooms) could prevent viral spread, contamination of radiotherapy clinics and other hospital spaces, and could be cost effective. The benefit-to-risk ratio is especially high for the elderly patients, who are more susceptible to complications from COVID-19 and less likely to develop radiation-induced cancers[25]. Whereas the radiobiologic response remains to be explored further in COVID-19 pneumonia[26], the implementation of a safe, illness-reducing therapy delivered with c-arm technology could be immediately implemented. Patients in low- to middle-income countries could have access to a viable life-saving treatment until a more definitive cure becomes available.

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