

Teaching Case

Regional Lymph Node Irradiation in Breast Cancer May Worsen Lung Damage in Coronavirus Disease 2019 Positive Patients



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Radiation-induced interstitial pneumonitis (IP) is a rare but possibly severe toxicity after radiation therapy (RT) in patients with comorbidities treated for breast cancer. Minimal symptoms are generally seen in the majority of patients and are resolved with short-term steroid administration. Since the introduction of treatment planning based on 3-dimensional conformal RT, IP risk has been significantly reduced with the application of rigorous lung constraints. With the use of modern techniques and hypofractionation, <2% of patients have experienced IP symptoms after a median follow-up of 15 months with ipsilateral lung V30 as the most relevant dosimetric predictor for IP risk.^{1,2} However, dose delivered to the ipsilateral lung, comorbidities, and virus infection could change the outcome of patients infected by Coronavirus Disease 2019 (COVID-19) during RT.

In this report, we describe a 73-year-old woman with a severe COVID-19 pneumonia infection diagnosed during RT for breast cancer. The main comorbidities were

obesity (body mass index 40 kg/m²), hypertension, and thrombosis after surgery for knee prosthesis.

The patient had right breast conservative surgery with sentinel node biopsy. The final pathology report suggested invasive carcinoma, grade II, without lymphovascular invasion, without ductal carcinoma in situ component, hormone receptor positive, and human epidermal growth factor receptor 2 negative. The surgical margins were clear. One of the 3 nodes removed was involved by macro metastasis and extracapsular extension. The positron emission tomography computed tomography (CT) and planning CT scan did not show any abnormalities in the lung (Fig 1A).

After oncogeriatric evaluation, the patient received 4 cycles of paclitaxel and cyclophosphamide combination. Adjuvant RT was planned to deliver 45 Gy in 18 fractions of 2.5 Gy (4 fractions a week) to the whole breast, supraclavicular, and internal mammary chain followed by a 15 Gy-boost to the tumor bed. Mixed photons and electrons beams were used for nodal RT. In terms of ipsilateral lung constraints, mean ipsilateral lung dose, V20 Gy, and V30 Gy were 18 Gy, 36%, and 18%, respectively (Fig 2).

During RT, at a dose of 35 Gy (day 1), the patient had a cough and fever. After confirmation of COVID-19 test positivity in D1, RT was suspended. On day 4 after the

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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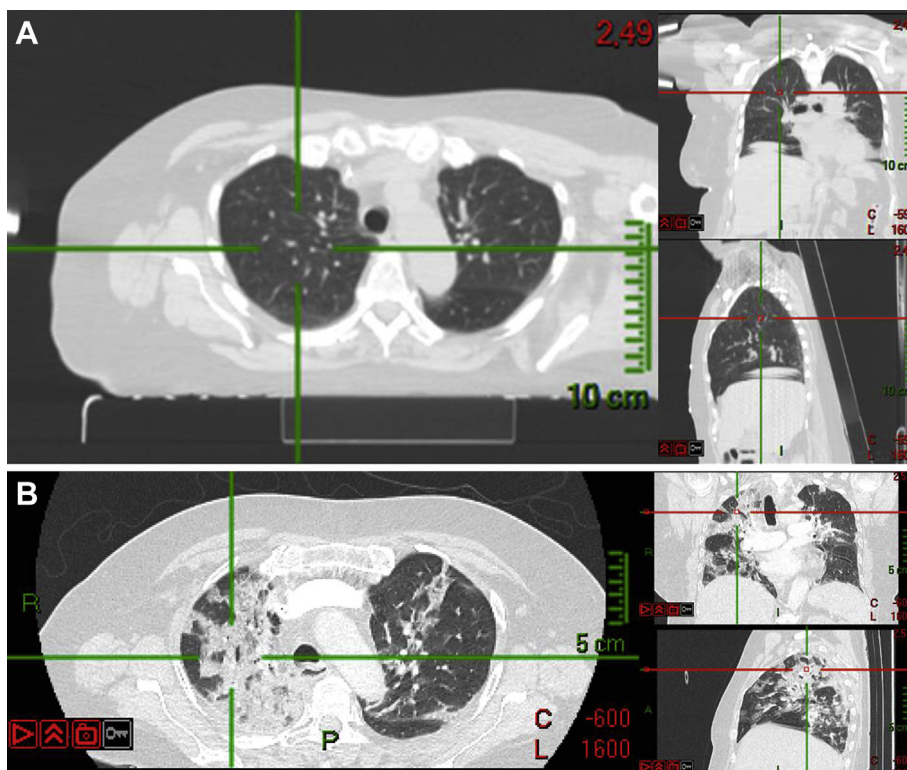


Figure 1 Computed tomography scan imaging. (A) Computed tomographic scan simulation planning. (B) Coronavirus disease 2019 diagnosis computed tomographic scan.

beginning of the symptoms, she was hospitalized given the need for oxygen therapy. Between days 10 and 13, oxygen dependence increased up to 15 L with continuous positive airway pressure. On day 12, and after 7 days of amoxicillin-clavulanate, corticosteroid treatment was introduced at a dose of 120 mg. Chest CT showed severe lung damage (50%-75%) with ground-glass opacities and a “crazy paving” pattern,³ without pulmonary embolism.¹ Figure 1B show ipsilateral damage seen on the same slice level on the CT scan performed after COVID-19 infection confirmation.

In the frame of our morbi-mortality review program,⁴ we reviewed the whole procedure and focused on the potential relationship between the severity of lung damage and irradiated lung volume. Figure 3A and B shows the image fusion between dose distribution and isodose curves on the planning CT scan and CT scan with COVID-19 lung damage.

CT scans fusion and review showed a significant correlation between the extent of the typical COVID-19 lung damage and irradiated right lung volume, in particular in the upper lobe of the right lung. On the COVID-19

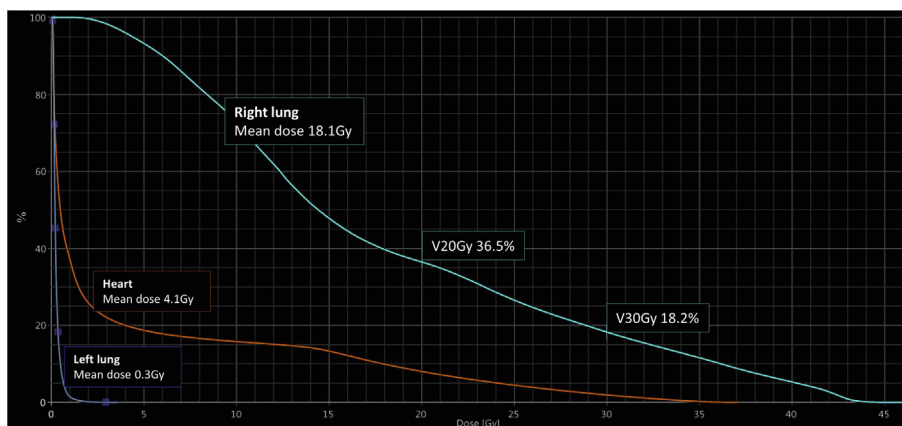


Figure 2 Dose volume histogram for ipsilateral lung.

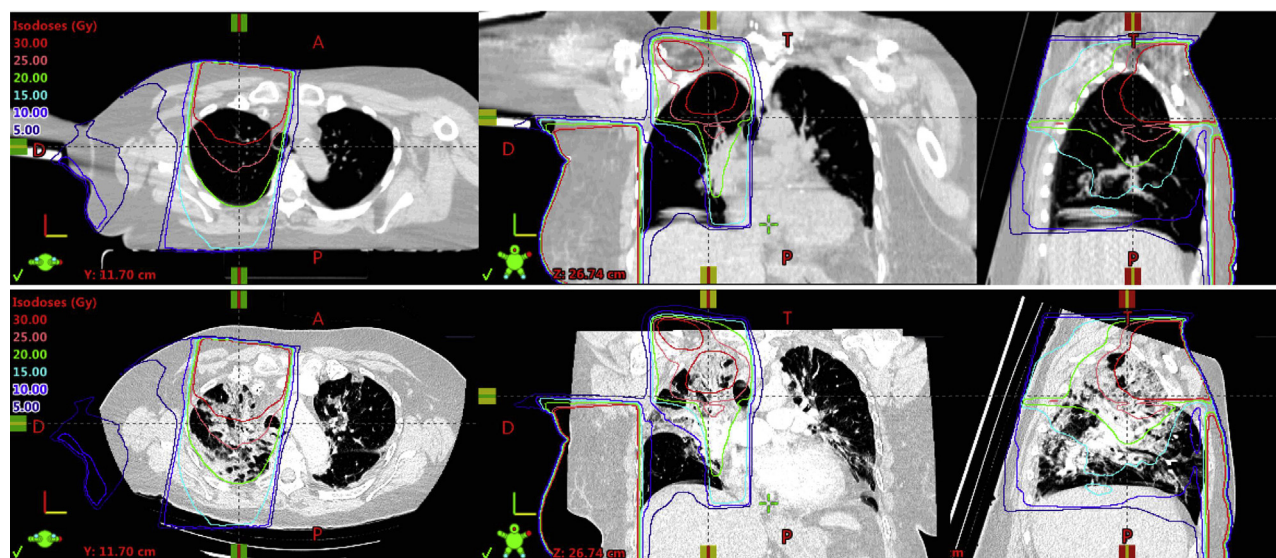


Figure 3 Lung dose distribution. (A) Isodose lines on the computed tomographic scan simulation planning. (B) Isodose lines on the coronavirus disease 2019 diagnosis computed tomographic scan.

CT scan (Fig 1B), the estimated ratio between COVID-19 lung damage and the healthy right lung was 54% (779 mL/1455 mL), although this ratio was estimated at 20% for the left lung (248 mL/1177 mL).

Table 1 show V5 to V30 values obtained from the fusion between dosimetry CT and COVID-19 CT scans. In summary, for low ranges of isodoses volumes (V5 and V20), the ratio between the damaged and the healthy lungs as delineated on the COVID-19 CT scan ranged between 54% and 59%. Furthermore, Fig 3A and B shows the projection of V5 to V30 isodose lines on the healthy lung delineated on the simulation CT scan and on the lung lesions induced by COVID-19 as seen on the COVID-19 CT diagnosis. The majority of the lung images are covered isodoses lines of V10 to V20.

Discussion

In daily practice, patients undergoing RT may be infected with COVID-19 at any time during treatment.

Their identification is crucial not only to avoid contamination of staff and other patients, but also to monitor carefully their state of health with the risk of respiratory distress. Among the risk factors reported in the literature, the irradiated lung volume is not studied. On the other hand, it is known that 20% to 40% of the patients develop unilateral CT scan COVID-19 lung damage, although both lungs could be concerned in the other patients.⁵

In breast cancer RT, the lung volume is greater when regional nodal irradiation is indicated. In the present case, as shown in Fig 3B, COVID-19 induced lung damage is predominant in the irradiated areas, although limited images are seen in the left lung. This is correlated to the right lung volume coverage by isodose lines as showed in the comparison presented Fig 4.

Given the lack of data concerning the effect of RT on the severity of COVID-19 lung damage, it seems important to remain extremely careful in cases receiving RT that partly involve the lungs, such as whole breast cancer ± nodal areas that include additional lung volume.^{6,7} Thus, it seems of paramount importance to point out the risk of

Table 1 Isodose distribution in the damaged versus healthy right lung

Isodoses (Gy)	Total right lung volume defined from the planning CT scan (mL)	Total right lung volume defined from the COVID-19 CT scan (mL)	Volume of damaged right lung defined from the COVID-19 CT scan (mL)	Ratio (%)
V5	1520	1342	728	54
V10	1181	1067	620	58
V15	779	670	397	59
V20	595	502	284	56
V25	434	362	175	48
V30	297	258	99	38

Data obtained from coronavirus disease 2019 (COVID-19) and planning computed tomography (CT) scans fusion.

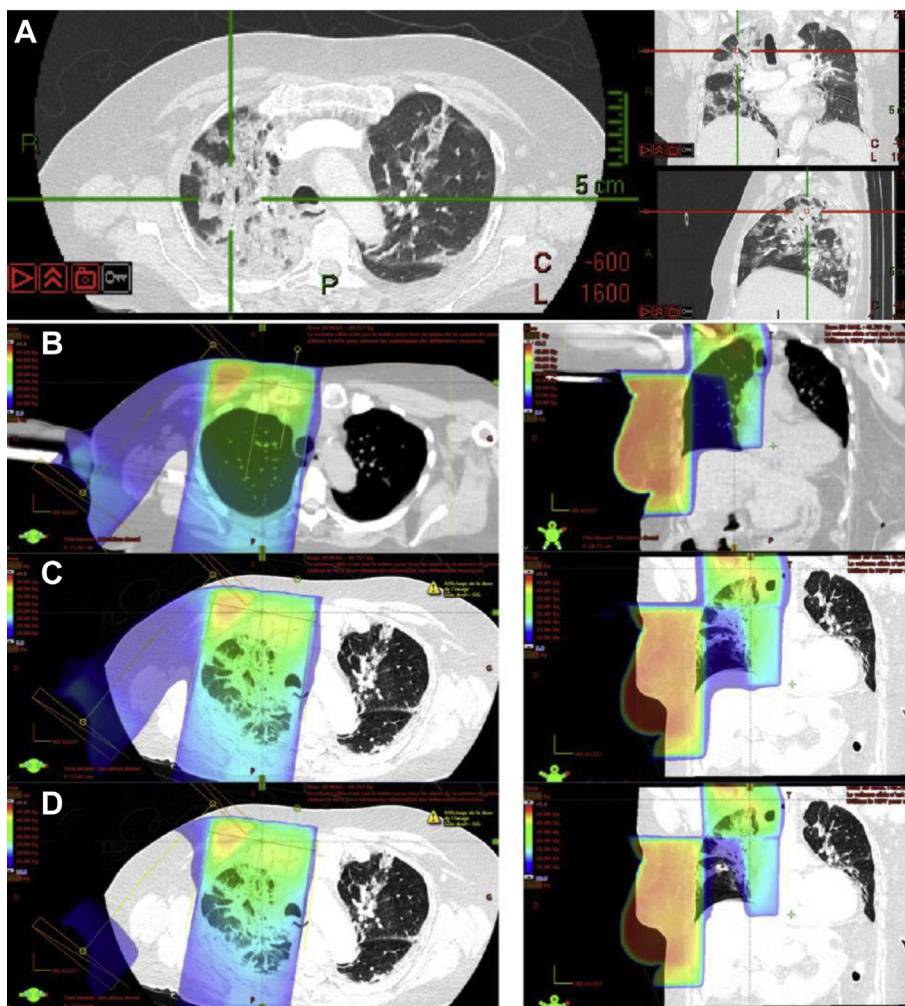


Figure 4 Comparison of dose distribution (V5 and V10). Interpretation: (A) chest computed tomographic performed at D12: severe lung damage (50%-75%) with ground-glass opacities and crazy paving pattern (3). Comparison with planning computed tomography with 5 Gy isodose (B) and coronavirus disease 2019 computed tomography with 5 Gy (C) and 10 Gy isodoses (D).

severe PI during RT for breast cancer in patients who became infected by COVID-19 during the period of their treatment. High caution for indications and volume definition is recommended when RT cannot be delayed in high-risk patients. In regional nodal irradiation cases, intensity-modulated radiation therapy (which increase only low doses), breathing adaptation and prone or lateral positioning may help to reduce ipsilateral lung exposure.^{8,9} However, prone or lateral position cannot allow adequate nodal coverage. Moreover, hypofractionation was reported to reduce lung dose irradiation.¹ Of note, our patient had moderate hypofractionated schedule due to her age and the distance between her home and our department.

It is known that COVID-19 disproportionally harms elderly persons and those with comorbid conditions.¹⁰ Moreover, in early reports from China, patients with cancer who acquired COVID-19 had a higher risk for

significant morbidity, including requirements for ventilatory support or death with a hazard ratio of 3.56.⁷ On the other hand, it is known that several parameters may influence incidence and severity of either radiation induced IP and COVID-19 severe acute respiratory syndrome. For this patient, unfortunately several risk factors for severe COVID-19 pneumonia, such as age >70 years, obesity, hypertension, cancer, and chemotherapy (with preexisting lymphopenia), were reported in her disease and personal history. She is still in an oxygen dependence situation with 15 L between D10 and D24.

Thus, in patients with BC undergoing RT, the utility of intervention must be weighed against the risk for inadvertent COVID-19 exposure in the health care system, especially during the initial weeks of the pandemic, when the risk for viral dissemination cannot be quantified and remains largely unknown.

Conclusions

In routine practice during the pandemic period, special attention is required to select high-risk BC patients who must start their RT without delay in particular those with triple negative, human epidermal growth factor receptor 2 positive and nodal involvement. The volume definition and organ at risk sparing, such as lung, is a crucial point to discuss. Any extended lung radiation could expose BC patients to a high risk of lung damage induced by COVID-19 infection. For patients receiving chemotherapy, lymphopenia is an additional risk factor for the severe form of COVID-19 lung infection. Thus, the decision to practice extended lymph node RT in these patients during the COVID-19 pandemic must be taken on a case-by-case basis, according to the ratio between benefit and risk.

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