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Regional lymph node irradiation in breast cancer may worsen lung damage in COVID-19 positive patients --Manuscript Draft--

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Abstract:	Radiation-induced interstitial pneumonitis (IP) is a rare after breast radiotherapy. Using modern techniques, IP risk has been significantly reduced. However, dose delivered to the ipsilateral lung, co-morbidities and virus infection could increase this risk particularly in patients infected by COVID-19 during RT. We report here evidence of a clear correlation between dose distribution in the ipsilateral lung and the COVID-19 lung damage shown in CT scan. Thus, it seems of paramount importance to point out the risk of severe IP during nodal 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.

Regional lymph node irradiation in breast cancer may worsen lung damage in COVID-19 positive patients

Running title: Breast radiotherapy in COVID-19 positive patiens

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Radiation-induced interstitial pneumonitis (IP) is a rare but possibly severe toxicity after radiotherapy (RT) in patients with co-morbidities 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 three-dimensional conformal RT (3D CRT), IP risk has been significantly reduced with the application of rigorous lung constraints. With the use of modern techniques and hypofractionation, less than 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, co-morbidities and virus infection could change the outcome of patients infected by COVID-19 during RT.

In this report, we describe a 73-year-old woman with severe COVID-19 pneumonia infection diagnosed during RT for breast cancer. The main comorbidities were obesity (BMI 40 kg/m²), hypertension and thrombosis following surgery for knee prosthesis.

The patient had right breast conservative surgery with sentinel node biopsy (SLNB). The final pathology report suggested invasive carcinoma, grade II, without lymphovascular invasion, without DCIS component, hormone receptor positive and HER2 negative. The surgical margins were clear. One of the three nodes removed was involved by macro metastasis and extracapsular extension. The PET-CT and planning CT scan did not show any abnormalities in the lung (Figure 1A).

After Oncogeriatric evaluation, the patient received four cycles of paclitaxel and cyclophosphamide combination. Adjuvant RT was planned to deliver 45Gy in 18 fractions of 2.5Gy (4 fractions a week) to the whole breast, supraclavicular and internal mammary chain, followed by a 15Gy-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, V20Gy and V30Gy were 18Gy, 36% and 18%, respectively (Figure 2).

During RT, at a dose of 35Gy (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 beginning of the symptoms, she was hospitalized given the need for oxygen therapy. Between days 10 and 13, oxygen dependence increased up to 15 liters 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. Figures 3A and B show 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 CT scan (Figure 1B), the estimated ratio between COVID-19 lung damage and the healthy right lung was 54% (779 cc/1455cc) while this ratio was estimated at 20% for the left lung (248cc/1177cc).

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, Figures 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 carefully monitor 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 20-40% of the patients develop unilateral CT scan COVID-19 lung damage, while both lungs could be concerned in the other patients (5).

In breast cancer RT, the lung volume is greater when regional nodal irradiation (RNI) is indicated. In the present case, as shown in Figure 3B, COVID-19 induced lung damage is predominant in the irradiated areas while 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 Figure 4.

Given the lack of data concerning the impact 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 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 RNI cases, IMRT (which increase only low doses), breathing adaptation and prone/lateral positioning may help to reduce ipsilateral lung exposure (8, 9). However, prone/lateral position can not 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 liters 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.

Conclusion

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, HER2 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.

References

- 1. Lee BM, Chang JS, Kim SY, Keum KC, Suh CO, Kim YB. Hypofractionated radiotherapy dose scheme and application of new techniques are associated to a lower incidence of radiation pneumonitis in breast cancer patients. Front Oncol. 2020 Feb 11;10:124. doi: 10.3389/fonc.2020.00124. eCollection 2020.
- 2. Werner EM, Eggert MC, Bohnet S, Rades D. Prevalence and characteristics of pneumonitis following irradiation of breast cancer. Anticancer Res. 2019 Nov;39(11):6355-6358. doi: 10.21873/anticanres.13847.
- 3. Rossi SE, Ersmus JJ, Volpachio M et al. "Crazy-Paving" Pattern at Thin-Section CT of the Lungs: Radiologic-Pathologic Overview. Radiographics 2003; 20(6):1509-20.

4. XXXXXXXXX.

- Ai T, Yang Z, Hou H etb al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020; <u>https://doi.org/10.1148/radiol.2020200642</u>
- 6. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11.
- Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335-337. [PMID: 32066541] doi:10.1016/S1470-2045(20)30096-6
- 8. Aznar MC, Duane FK, Darby SC, Wang Z, Taylor CW. Exposure of the lungs in breast cancer radiotherapy: A systematic review of lung doses published 2010-2015. Radiother Oncol. 2018;126(1):148-154. doi: 10.1016/j.radonc.2017.11.022. Epub 2017 Dec 12.
- Belkacemi Y, Loganadane G, Ghith S, et al. Axillary nodal irradiation practice in the sentinel lymph node biopsy era: Comparison of the contemporary available 3D and IMRT techniques. Br J Radiol. 2020 Apr 1:20190351. doi: 10.1259/bjr.20190351. [Epub ahead of print]
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395:507-513. [PMID: 32007143] doi:10.1016/S0140-6736(20)30211-7

Figure Legends

Figure 1. CT scan imaging

(A) CT scan simulation planning(B) COVID-19 diagnosis CT scan

Figure 2. Dose Volume Histogram (DVH) for ipsilateral lung

Figure 3. Lung dose distribution

(A) Isodose lines on the CT scan simulation planning

(B) Isodose lines on the COVID-19 diagnosis CT scan

Figure 4. Comparison of dose distribution (V5 and V10)

Interpretation:

(A) Chest CT performed at D12: severe lung damage (50-75%) with ground-glass opacities and crazy paving pattern (3). Comparison with planning CT with 5Gy isodose (B) and COVID-19 CT with 5Gy (C) and 10Gy isodoses (D).

Isodoses (Gy)	Total right lung volume defined from the	Total right lung volume defined from the	Volume of damaged right lung defined from the	Ratio (%)
	planning CT scan (cc)	COVID-19 CT scan (cc)	COVID-19 CT scan (cc)	
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

Table 1. Isodose distribution in the damaged versus healthy right lung.Data obtained from COVID-19 and planning CT scans fusion

V5 to V30: volume receiving 5-30Gy; Ratio: % of damaged lung volume out of the total lung volume delineated on the COVID-19 CT scan.









Figure 4.

