Editorial Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.2023113218-221

Editorial Comment to: Lung-heart Toxicity in a Randomized Clinical Trial of Hypofractionated Image-guided Radiation Therapy for Breast Cancer

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Post-operative adjuvant radiotherapy plays a key role in controlling and preventing the local recurrence and mortality of breast cancer.[1] However, patients may suffer from long-term effects including the development of new types of cancer and damage to organs. The lung and heart are the two most critical organs significantly affected by radiotherapy for breast cancer because of their location next to the breast, and because they work intricately together to accomplish the function of moving oxygen from ambient air to the tissues, exchanging with carbon dioxide. In this editorial, we comment on the necessity of tandem sparing of the lungs and heart. Firstly, we recall key characteristics of cardio-pulmonary physiology. Secondly, giving credit where credit is due, we recall historical signposts of breast radiotherapy toxicity to lungs and heart. Thirdly, we present evidence that the toxicity can be significantly reduced with modern radiotherapy. Lastly, we reflect on the challenges to future research in breast radiotherapy.

Lungs and heart interdependence

The intricate interplay between cardiac and lung physiology is vital, governing processes within the cardiovascular and respiratory systems. The heart propels oxygenated blood rich in nutrients throughout the body while removing metabolic waste. Simultaneously, deoxygenated blood returns to the heart for oxygenation in the lungs. The lungs facilitate gas exchange, extracting oxygen and expelling carbon dioxide through breathing. This exchange occurs in the alveoli, tiny air sacs in the lungs. The interaction between the lung and the heart involves direct ventricular interaction, blood volume redistribution, and left ventricular afterload regarding the physiology[2] or through the relationship between pulmonary and cardiac diseases.[3] Assessing the heart's function involves gathering patient history, checking vital signs (blood pressure, heart rate) and examination. In examination, the peripheral pulses and jugular venous pressure are evaluated, and auscultation is performed to listen for heart sounds and blood flow. We can use many types of tests to assess heart functions. We can check its electricity (ECG), pumping capacity (Echocardiogram), cardio function under stress (Stress Test), cardiac enzyme markers, structural assessment (MRI or CT scan). Pulmonary function assessment includes both clinical and non-clinical modalities, similar to the approach taken in heart assessment. Clinical methodologies involve thorough patient history collection, evaluation of respiratory patterns, oxygen saturation, and physical examinations employing inspection, palpation, and auscultation. In the non-clinical techniques such as spirometry, peak flow rate measurement, X-ray and advanced imaging modalities like CT scans, MRI, PET and V/Q scans are employed to provide a thorough understanding of pulmonary function.

When lung function is not working well due to conditions like chronic bronchitis, pneumonia, or pneumonitis, the gas exchange becomes less efficient. This inefficiency leads to lower oxygen levels in the blood and a buildup of carbon dioxide, causing problems like difficulty breathing and reduced ability

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to exercise. At the same time, if the heart is not working properly due to issues like heart failure or coronary artery disease, it affects the flow of blood throughout the body. The heart, responsible for pumping oxygen-rich blood to different organs, struggles to meet the body's needs. This can result in tiredness, retaining fluids, and, in severe cases like organ failure. Of importance, there is considerable overlap in the assessment of the heart and pulmonary symptoms.

There are many factors that can damage lung and heart functions. They may be internal factor stemming from comorbidities which play a key role in developing long-term impacts on the lungs and heart, such as diabetes, cardiac disease, hypertension, previous surgeries[4] and systemic treatment.[5] They can be external such as pollution, smoking and substance expose (asbestosis or coal), even common environmental exposes via the link with extracellular vesicles causing chronic systemic lung and heart diseases.[6] As a reminder, the lungs have been dramatically at the forefront during the COVID-19 pandemics, stressing the importance of sparing the lungs.[7-9]

The overall message is that lung and heart physiology are complex. Relying on a single “toxicity grade” might be misleading. The functional evaluation is multidimensional. We will refer to that later.

Historical signposts, from toxicities to improved overall survival

It has been known over a hundred years ago, almost immediately after Roentgen discovery of X-rays, as early as 1909, that radiation was efficient to control breast cancer and reduce recurrence.[10,11] However, a favorable effect on survival has long been elusive. It was shown in 1987 that excess deaths occurred among patients receiving post-operative radiotherapy.[12] Building on the 1995 meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG),[13] in 2000 Van de Steene *et al.* were the first to demonstrate a significant overall survival benefit,[14] which the EBCTCG acknowledged soon after.[15] Van de Steene *et al.* stressed that the benefit was contingent on the use of current techniques to reduce cardiovascular and other toxicities.[14] The authors did not specify what they meant by “other toxicities”. But to radiation oncologists at the time, lung damage was a well-known major toxicity demonstrated in numerous studies.[16-19] A subsequent pooled analysis for breast conserving surgery found in 2004 a two-third proportional reduction of local-regional recurrences, but with a small benefit in overall survival,[20] rejoining Van de Steene *et al.* that there was an urgent need to consider better radiation techniques than those used at the time. Interestingly, the latest EBCTCG regional nodes radiotherapy meta-analysis,[21] in 2023, restated almost word-for-word what Van de Steene *et al.* had already observed in 2004, that the overall survival benefit was a characteristic of the more recent trials.[22]

Reducing lung-heart toxicity with modern radiotherapy

The signposts recalled above led to the design of TomoBreast, a randomized clinical trial conducted in 2007-2011 that compared hypofractionated image guided radiation therapy (H-IGRT), delivered with the tomotherapy system, with normofractionated conventional radiation therapy (CRT), delivered with 3D conformal therapy.[23] H-IGRT patients received 42 Gy to the breast/chest wall with/without nodal irradiation and simultaneous integrated boost to 51 Gy in 15 fractions over 3 weeks. CRT patients received 50 Gy to the breast/chest wall with/without nodal irradiation in 25 fractions over 5 weeks and 16 Gy sequential boost in 8 fractions over 1.6 weeks. The trial hypothesized that H-IGRT could provide a significant reduction in lung and heart toxicity, as compared with CRT. Reminding that lung and heart assessments are multidimensional, measurements were made using patient reported outcome (PRO), Radiation Therapy Oncology Group (RTOG) toxicity score, left ventricular ejection fraction (LVEF), and pulmonary function tests (PFT). In an intention-to-treat analysis at 12 years median follow-up, the survival time free from alteration in any of the measured outcomes was significantly improved with H-IGRT, P=0.041, providing a gain of restricted mean survival time free of alteration of 1.46 years as compared with CRT. This study is the only one to date that demonstrates the positive impact of H-IGRT globally on cardio-vascular, pulmonary function and quality of life in breast cancer adjuvant radiotherapy, without causing disease-free survival reduction.

Challenges to future breast cancer radiotherapy research

TomoBreast is a proof of concept that technology matters in the radiotherapy of breast cancer. There are, however, drawbacks to the tomotherapy system: notably treatment duration is long,[24] and the system cannot manage breathing control which has attracted considerable attention.[25] Beyond tomotherapy, the current challenge is to identify the most cost-effective technique to improve the balance of tumor control and avoidance of toxicity. Another challenge is that most of the later decade has been devoted to reducing the risk of heart toxicity with little attention to the lungs.

It is not the purpose of this commenting editorial to review or to advocate any particular technique, but to point out that the lungs have an intertwined physiological importance in tandem with the heart. Future research will have to consider not the heart or the lungs exclusively, but both the lungs and the heart.

CONFLICTS OF INTEREST

The editorial was written based on experience and knowledge of the team without receiving any commercial or financial relationships which can potentially create conflicts of interest.

ACKNOWLEDGEMENTS

None.

FUNDING

There is no funding for this work to declare.

ACKNOWLEDGMENTS

None.

ETHICAL CONSIDERATIONS

Not applicable.

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How to Cite This Article

Nguyen MD, Vinh-Hung V, Storme G. Editorial Comment to: Lung-heart Toxicity in a Randomized Clinical Trial of Hypofractionated Image-guided Radiation Therapy for Breast Cancer. Arch Breast Cancer. 2024; 11(3):218-21.

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