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EDITORIAL COMMENT

Deep Inspiration Breath Hold for Cardiac Sparing

No Deep Pockets Required

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Breast cancer mortality has plummeted in many countries thanks to advances in screening, surgical and radiotherapy (RT) techniques, and systemic therapies.[1] Although the 50% relative recurrence risk reduction associated with RT has remained consistent in clinical trials, the absolute locoregional control and survival benefits associated with RT are becoming increasingly modest as patient outcomes improve.[2] Given the global burden of breast cancer, with a predicted 3 million new diagnoses annually by 2040,[3] even modest benefits meaningfully impact a large number of individual patients.

Optimizing the therapeutic ratio remains a fundamental tenet of radiation oncology philosophy with an emphasis on weighing treatment benefits against long-term complications. Darby et al[4] reported a relative 7.4% increase in major coronary events per additional 1 Gy of mean heart dose (MHD) with no lower threshold and higher absolute excess risk in patients with pre-existing risk factors. Inspired by the long survivorship of their patients, breast radiation oncologists are leaders in leveraging improvements in RT planning and delivery techniques to reduce cardiac doses to a small fraction of what is commonly accepted in other thoracic disease sites.[5]

The deep inspiration breath hold (DIBH) technique is 1 of many cardiac-sparing RT techniques. Precise delivery of RT using DIBH requires specialized equipment and operational procedures that affect clinical workflow. DIBH patients typically undergo 2 computed tomography simulation scans instead of 1 (free-breathing [FB] and DIBH scans), longer treatment planning time, increased image-guided radiation therapy requirements for accurate positioning, and increased treatment time. These incremental changes add up to nontrivial increases in time, infrastructure, and cost.

Although the dosimetric advantages of DIBH are well established, its impact on cardiovascular disease and cost-effectiveness is an area of ongoing research.[6] In this issue of *JACC: CardioOncology*, the study by Busschaert et al[7] is an important addition to the literature whereby left DIBH and FB breast RT plans were generated for 100 patients. The average MHDs were calculated, and cardiac toxicity was estimated. Rigorous modeling and simulations were performed to evaluate DIBH cost-effectiveness by comparing the estimated operational, financial, and cardiac outcomes of DIBH vs FB RT. The effect of DIBH on cardiovascular disease risk was used to calculate differences in quality-adjusted life-years (QALYs). Acknowledging the long-term effect of RT on cardiovascular disease, their model used a 20-year time horizon, included baseline cardiovascular disease risk factors, distinguished between fatal and nonfatal cardiovascular events, and was run 10,000 times to achieve 95% CIs.

The results demonstrated MHDs of 4.33 Gy in FB vs 1.78 Gy in DIBH plans with an absolute risk reduction of 1.72% in cardiovascular events and 0.69% in fatal events. This dose is similar to the 4.4-Gy MHD reported in a meta-analysis on cardiovascular disease.[8] Additionally, the 0.69% reduction in cardiovascular disease mortality risk with DIBH in the current study is similar to the 0.3% to 1.2% cardiovascular disease

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excess mortality attributed to RT in the meta-analysis,[8] raising the question of whether DIBH could essentially negate the cardiovascular disease risk associated with RT. The benefits of DIBH do come with a cost, with a 12.5% decrease in departmental throughput and a €617 mean increase per patient. This translates to an incremental cost-effectiveness ratio of €14,023/QALY over 20 years, well below the willingness-to-pay threshold of €40,000/QALY, suggesting that DIBH is cost-effective in the specific context in which it was tested.

Reflecting current RT practices, multiple dose fractionation regimens were used. It is not clear whether MHD estimates in this study reflected adjustments for the biological effective dose, which could cause underestimation of true MHD in hypofractionated regimens, potentially leading to an understatement of DIBH cost-effectiveness. Although this study's FB MHD of 4.33 Gy is consistent with historical trials,[8] radiation oncologists in some settings typically achieve MHD <2 Gy even without DIBH[9]; this difference underscores regional practice differences, which could influence DIBH cost-effectiveness. Additional information we hope the authors or others may address in the future include the impact of a volumetric modulated arc therapy (VMAT) boost on MHD, RT field targets (eg, internal mammary nodes), and chemotherapy use given the synergistic cardiotoxic effects of RT with anthracyclines and trastuzumab. We also agree with the authors that future research to examine the generalizability of their findings in centers that differ from their own would be valuable.

Not all patients are suitable DIBH candidates because of the physical, psychological, and linguistic requirements. Older age, high body mass index, language barriers, and respiratory or psychological disorders can hinder a patient's ability to perform DIBH; this is especially unfortunate because these populations likely have higher baseline cardiovascular disease risk and would stand to benefit most from DIBH. Similarly, just as minoritized race has been associated with a lack of timely access to RT, clinical trials, hypofractionation, increased toxicity, and worse oncologic outcomes,[10] Black women in the United States have been shown to have reduced access to cardiac-sparing techniques such as DIBH.[11] Busschaert et al's findings[7] underscore the need to ensure equitable access to this key cost-effective strategy for eligible patients.

Although DIBH is one way to achieve cardiac sparing, multiple alternative options exist, especially in node-negative patients. These include partial breast irradiation, prone positioning, and modified tangents whereby RT fields are designed to block the heart at the expense of low-risk breast tissue. Other approaches include highly conformal techniques such as VMAT and proton therapy, although protons are expensive and can be logistically inconvenient, suggesting its use is likely most appropriate in advanced disease necessitating internal mammary node targeting because of their close proximity to the heart, a setting in which it is currently being investigated. Finally, the omission of RT altogether may be a reasonable option in carefully selected, low-risk patients.[12]

Of note, MHD is the most commonly studied dosimetric parameter, but whether it is the best predictor of cardiac toxicity remains unclear. MHD is a crude metric that can vary widely with technique (eg, VMAT vs 3-dimensional conformal radiation) and may actually be a surrogate for cardiac substructures such as the left anterior descending artery and left ventricle, which could provide more accurate predictions of long-term cardiac toxicity.[13,14] Current prospective trials are expanding their dosimetric analyses beyond the MHD. Future studies should evaluate the impact, including the cost-effectiveness, of various approaches for cardiac sparing and may benefit from more sophisticated models incorporating considerations of substructure doses that could emerge in the future.

Although ongoing questions remain regarding the optimal approach to cardiac sparing in breast RT, the authors deserve recognition for their meaningful contribution to the literature. Cost-effectiveness is an exceptionally complex area of research, especially regarding long-term toxicity outcomes such as cardiovascular disease, with myriad implications for clinical practice and policy. With the ever-surging health care costs, new treatment techniques must be critically evaluated and thoughtfully implemented with considerations not only for safety and efficacy but also for economic efficiency. Information to this end is essential for the careful allocation of scarce societal resources to ensure appropriate access and equity of care delivery.

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