



Radiotherapy benefits outweigh risks for breast cancer in modern era

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Comment on: Taylor C, Correa C, Duane FK, *et al.* Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. *J Clin Oncol* 2017;35:1641-9.

Submitted May 15, 2017. Accepted for publication May 23, 2017.

doi: 10.21037/tcr.2017.06.24

View this article at: <http://dx.doi.org/10.21037/tcr.2017.06.24>

The detrimental effects of smoking are well-known. Public health measures have focused on the prevention of tobacco use and cessation of its use. The prevalence of smoking was influenced not merely by social customs but tobacco control policies as well. Most men in many parts of Asia and central and Eastern Europe smoke (1). There are more women in Europe smoke than women in other regions. The male and female smoking prevalence have become virtually the same in some European countries (2). There is the highest prevalence of smoking among women in Western societies. It is about 40% in some European countries. The mortality rate of lung cancer continues to rise among continental European women (3).

For smokers with breast cancers, their smoking habits may interfere with the therapeutic gain and result in excess acute toxicity. Taylor *et al.* (4) reported a meta-analysis this March. They estimated that the absolute risks from modern radiotherapy (RT) to develop lung cancer were approximately 4% for long-term continuing smokers and 0.3% for nonsmokers. As for cardiac mortality, the absolute risks were approximately 1% for smokers and 0.3% for nonsmokers. As for acute toxicity, Pignol *et al.* (5) conducted a study to show that smoking caused severe moist desquamation and pain associated with postmastectomy radiation therapy. Skin toxicity doubled for smokers, with 40% severe pain, 48% grade 3 moist desquamation, and 64% grade 3 skin toxicity.

RT for breast cancer patients has been one of the crucial treatment approaches. For patients after breast-

conserving surgery, it reduced the 10-year recurrence risk and the 15-year risk of breast cancer death (6). For patients after mastectomy and axillary dissection with positive nodes, RT reduced 10-year recurrence and 20-year breast cancer mortality (7). The benefits of RT are substantial. However, the concern regarding damages to lung or heart remains (8). Darby *et al.* (9) conducted a population-based case-control study of major coronary events in 2,168 women who received RT for breast cancer between 1958 and 2001. They acquired the hospital records of myocardial infarction, coronary revascularization, or death from ischemic heart disease and estimated the mean radiation doses to the whole heart and to the left anterior descending coronary artery from these patients' RT chart. For the first time, they described that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (95% confidence interval, 2.9–14.5; $P < 0.001$). They calculated that the overall average of the mean doses to the whole heart was 4.9 (range, 0.03 to 27.72) Gy using the technology available between 1958 and 2001. Taylor *et al.* (10) indicated that the largest radiation doses were received by the anterior part of the heart and the left anterior descending coronary artery in most techniques. Irradiation of these structures might have added to the surplus risk of death from heart disease seen after some past breast cancer RT regimens. It is imperative to evaluate the treatment-related late effects and to decrease such risks by minimizing the dose delivered to normal tissues.

The exposure of the heart to ionizing radiation during RT for breast cancer can be lowered significantly using many different technologies nowadays. According to Taylor *et al.* (4), the mean doses from 647 regimens published during 2010 to 2015 were 5.7 Gy for whole lung and 4.4 Gy for whole heart. The median year of irradiation was 2010 [interquartile range (IQR), 2008 to 2011]. In other words, the mean dose to whole heart was lowered about 0.5 Gy in the past decade comparing with that before the millennium.

There are numerous methods to optimize the delivery of ionizing radiation. Radiation oncologists use computerized tomography simulation (CT-sim) to contour target volumes and adjacent organs at risk. The lung and heart volumes can be identified and the exposure to ionizing radiation can be calculated via computerized treatment planning. In whole breast radiation, we delineate the entire breast tissue as target and prescribe a dose of 50 Gy in 25 fractions. Typical boost doses to surgical bed are 10–16 Gy in 4–8 fractions.

Some may prescribe simultaneous integrated boost (SIB) to shorten the whole RT course. There were researchers comparing SIB intensity-modulated radiation therapy (SIB-IMRT) with 3-dimensional conformal RT (3D-CRT) using opposed tangential fields. SIB-IMRT reduced the mean dose, maximum dose, and the V20 to lung by 55–104 cGy, 983–1,298 cGy ($P<0.001$), and 3.7–4.4%, respectively (11).

There were scientists comparing Helical Tomotherapy with 3D-CRT. They found that ipsilateral lung V20 (6.34% *vs.* 10.17%; $P<0.001$), V5 (16.54% *vs.* 18.53%; $P<0.05$) and the mean dose to the lung (4.05 *vs.* 6.36 Gy; $P<0.001$) were significantly lower. In patients with left-sided tumors, heart V30 (0.03% *vs.* 1.14%; $P<0.05$) and the mean dose to heart (1.35 *vs.* 2.22 Gy; $P<0.01$) were significantly lower with Helical Tomotherapy, but not V5. Yet, contralateral breast V5 (0.27% *vs.* 0.00%; $P<0.01$) and maximum dose were significantly increased with Helical Tomotherapy (12).

When volumetric modulated arc therapy (VMAT) was employed and compared with IMRT, The V5, V10 and mean dose to ipsilateral lung were significantly higher than IMRT ($P<0.05$) and IMRT with electron boost ($P<0.05$). The mean dose, V5 and V10 to heart with VMAT were significantly greater than those of IMRT and IMRT with electron boost ($P<0.05$) (13). There were researchers sharing more results from the comparison of IMRT, VMAT and a tangential VMAT (tVMAT), each with and without flattening filter. tVMAT had the significantly lowest doses to the contralateral organs at risk with a mean dose of 0.7 ± 0.1 Gy for the contralateral lung, 1.0 ± 0.2 Gy for the

contralateral breast and 1.4 ± 0.2 Gy for the heart (14).

Respiratory control techniques including deep inspiration breath-hold (DIBH) further reduce dose to the heart and lung. Some studies illustrated the significant reduction of cardiac doses from IBH compared to that with free breathing (15–18). The NTCP for cardiac mortality could be decreased by about 78 % ($P=0.017$) (19). Lately, Koivumaki *et al.* (20) demonstrated the geometrical uncertainty of heart position in DIBH RT of left-sided breast cancer patients and suggested adding margins to heart contour in order to avoid the unnecessary doses to heart.

On occasion, simply change of positioning caused better conformity indices, target dose distribution and sparing of the heart and lung. Mulliez *et al.* (21) compared dosimetry of wedged tangential fields, tangential field IMRT and multi-beam IMRT in prone and supine positions for whole-breast irradiation. Prone IMRT lowered lung and heart doses significantly. It is superior to any supine treatment. In addition, the influence of planning techniques in the prone position is less distinct. Verification of daily setup consistency using prone position may be done with weekly imaging in order to decrease set-up errors.

While a number of studies confirmed the association between breast tumor irradiation and risk of undesirable doses to the heart and the lung causing lung cancer and cardiac morbidity. Investigators put a lot of time and effort in the attempt to reduce the doses to the heart and lungs during RT for breast cancer. Despite the hard work, there is also an ongoing prospective study for early detection and prediction of cardiotoxicity after RT for breast cancer (22). They aim to capture the early signs of cardiotoxicity that can appear long before the onset of any clinically significant cardiac events.

Conclusions

The benefits of RT compensate the risks for most nonsmokers and ex-smokers (4). This exploration allows people to better discern between RT-related risks and those generated by other confounding factors such as smoking. When the patient and family meets with the radiation oncologist and the clinical nurse coordinator to discuss their case in detail, this information is especially valuable in the patient consultation prior to RT. We encourage breast cancer patients to quit smoking so as to benefit more from RT.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor San-Gang Wu (Department of Radiation Oncology, Xiamen Cancer Center, the First Affiliated Hospital of Xiamen University, Xiamen, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.06.24>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Huang CJ, Lee HH. Radiotherapy benefits outweigh risks for breast cancer in modern era. *Transl Cancer Res* 2017;6(Suppl 6):S989-S992. doi: 10.21037/tcr.2017.06.24