In Reply to Struikmans et al

Mutter, Robert W; Choi, J Isabelle; Jimenez, Rachel B; Kirova, Youlia M; Fagundes, Marcio; Haffty, Bruce G; Amos, Richard A; Bradley, Julie A; Chen, Peter Y; Ding, Xuanfeng

Published in:
International Journal of Radiation Oncology Biology Physics

DOI:
10.1016/j.ijrobp.2021.12.155

Publication date:
2022

4. Moran AE, Forouzanfar MH, Roth G, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation* 2014;129:1483–1492.
5. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383:1838–1847.

In Reply to Struikmans et al.

To the Editor: We thank Struikmans et al for their interest in our consensus statement.[1] We are in agreement, as highlighted in multiple locations of our manuscript, that "advances have been made in photon cardiac sparing with techniques such as deep-inspiratory breath hold," which may reduce the absolute risk of breast cancer radiation therapy in the modern era.[2] In addition, improvements in cardiologic medicine are likely to lower the risk of cardiovascular events, including death, in those burdened with radiation-associated coronary disease in the years ahead.[3] Nevertheless, patients with chronic coronary disease are still at high risk of acute cardiovascular events.[3-5] Thus, preventing radiation therapy-associated cardiac disease remains of paramount importance, particularly given the advances in multidisciplinary breast cancer care, which have prolonged life expectancies of patients diagnosed with the disease.

The authors call into question the linear, no-threshold relationship between cardiac dose and major coronary events proposed by Darby et al and validated by others in large population-based studies.[6-8] To do so, they highlight 15-year results from the European Organization for Research and Treatment of Cancer (EORTC) 22922-10925 trial, which randomized patients to regional node irradiation (RNI) versus no RNI in patients with early-stage breast cancer. However, in this study the incidence of cardiac disease was significantly higher in those who received RNI, which increases cardiac dose. The cumulative incidence rate at 15 years for any cardiac disease was 9.4% (95% confidence interval, 8.0%-10.8%) versus 11.1% (95% confidence interval, 9.6%-12.7%) for those treated without or with RNI ($P = .04$), translating into a relative increase of approximately 18% with RNI. The increased cardiac morbidity partially off-set the small breast cancer mortality benefit of RNI observed in that study.[9]

This work was supported in part by K12 HD065987 (R.W.M.).

Disclosures: R.B.M.V. reports travel funds from Varian (2017) and IBA (2018). J.A.B. reports travel funds from IBA (2018). Unrelated to this manuscript, A.Y.H. has received research funding from Merck and GSK and received consulting fees from La Roche Posay. M.F. reports being a consultant for Augmenix and Boston Scientific related to lecturing and training of new users of rectal spacers. Unrelated to this manuscript, R.A.A. reports being on the scientific advisory board and receiving honoraria from TAE Life Sciences. X.D. has a patent related to spot-scanning proton arc therapy and this patent has been licensed to IBA.

The authors have previously acknowledged limitations in their ability to accurately estimate cardiac dose of individual patients who participated in the trial owing to a lack of computed tomography–based treatment planning.[8] According to the Darby model, the 18% relative increase in cardiac disease, as observed in the RNI arm of EORTC 22922-10925, would be predicted following approximately 2.5 Gy mean heart dose.[5] Such an increase in cardiac exposure might have been expected in the RNI arm. Interestingly, the absolute difference in cardiac disease between the 2 arms continues to diverge past 15 years (Fig. 2C from Poortmans et al[8]). We look forward to further follow-up for cardiac events, which are concentrated later in life, and applaud the authors for carrying out these detailed toxicity analyses. Nevertheless, the sum of the currently available data, including EORTC 22922-10925, support a causal relationship between cardiac dose and cardiac adverse events. In our consensus statement, we advocate for "additional work- . . .to better delineate the relationship among. . .dose volume parameters, systemic therapy, and host factors with various cardiac endpoints." However, the linear, no-threshold relationship between cardiac dose and radiation-associated cardiac events originally put forward by Darby et al remains the most evidence-based and patient-centered model to guide breast cancer radiation therapy. Moreover, the available data supports the use of cardiac sparing strategies, including proton therapy, to mitigate the risk of radiation-associated cardiac morbidity.

Robert W. Mutter, MD
Department of Radiation Oncology
Mayo Clinic
Rochester, Minnesota

J. Isabelle Choi, MD
Department of Radiation Oncology
New York Proton Center and Memorial Sloan Kettering Cancer Center
New York, New York

Rachel B. Jimenez, MD
Department of Radiation Oncology
Massachusetts General Hospital
Boston, Massachusetts

Youlia M. Kirova, MD
Department of Radiation Oncology
Institut Curie
Paris, France

Marcio Fagundes, MD
Department of Radiation Oncology
Miami Cancer Institute
Miami, Florida

Bruce G. Haffty, MD
Department of Radiation Oncology
Rutgers Cancer Institute of New Jersey
New Brunswick, New Jersey

Richard A. Amos, MSc, FIPEM
Proton and Advanced Radiotherapy Group
Department of Medical Physics and Biomedical Engineering
University College London
London, United Kingdom

Julie A. Bradley, MD
Department of Radiation Oncology
University of Florida
Jacksonville, Florida

Peter Y. Chen, MD
Xuanfeng Ding, PhD
Antoinette M. Carr, MD
Leslie M. Taylor, BSN, RN
Department of Radiation Oncology
Beaumont Health
Royal Oak, Michigan

Mark Pankuch, PhD
Department of Radiation Oncology
Northwestern Medicine Proton Center
Warrenville, IL

Raymond B. Mailhot Vega, MD, MPH
Department of Radiation Oncology
University of Florida
Jacksonville, Florida

Alice Y. Ho, MD
Department of Radiation Oncology
Massachusetts General Hospital
Boston, Massachusetts

Petra Witt Nyström, MD, PhD
The Skandion Clinic, Uppsala, Sweden and
Danish Centre for Particle Therapy
Aarhus, Denmark

Lisa A. McGee, MD
Department of Radiation Oncology
Mayo Clinic Hospital
Phoenix, Arizona

James J. Urbanic, MD
Department of Radiation Medicine and Applied Sciences
UC San Diego Health
Encinitas, California

Oren Cahlon, MD
Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center
New York, New York

John H. Maduro, MD, PhD
Department of Radiation Oncology
University of Groningen
University Medical Center Groningen
Groningen, The Netherlands

Shannon M. MacDonald, MD
Department of Radiation Oncology
Massachusetts General Hospital
Boston, Massachusetts

https://doi.org/10.1016/j.ijrobp.2021.12.155

References

1. Struikmans H, Mast ME, Petoukhova AL, Poortmans PM. In regard to Mutter et al. *Int J Radiat Oncol Biol Phys* 2022;112:1288.
2. Mutter RW, Choi JI, Jimenez RB, et al. Proton therapy for breast cancer: A consensus statement from the Particle Therapy Cooperative Group Breast Cancer Subcommittee. *Int J Radiat Oncol Biol Phys* 2021;111:337–359.
3. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383:1838–1847.
4. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–1722.
5. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319–1330.
6. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–998.
7. van den Bogaard VA, Ta BD, van der Schaaf A, et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. *J Clin Oncol* 2017;35:1171–1178.
8. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol* 2016;34:235–243.
9. Poortmans PM, Struikmans H, De Brouwer P, et al. Side effects 15 years after lymph node irradiation in breast cancer: Randomized EORTC Trial 22922/10925. *J Natl Cancer Inst* 2021;113:1360–1368.

Sparing the Parotid Stem Cells

In Regard to Steenbakkers et al.

To the Editor: We read the article titled "Parotid Gland Stem Cell Sparing Radiotherapy for Head and Neck Cancer Patients: A Double-Blind Randomized Controlled Trial" by Steenbakkers et al with great interest.[1] We recently published a cross-sectional study on the same issue and were looking forward to a prospective randomized trial.[2] Ipsilateral parotid gland function affected by the dose to both the contralateral parotid gland and stem cells is an important

Disclosures: none.