Cardiac disease and second lung cancer after radiotherapy for breast cancer

Candace R. Correa, Sarah C. Darby

Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford, Oxford, UK

Radiotherapy (RT) is an important tool in the multidisciplinary management of breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of randomised clinical trials demonstrated that the addition of RT to breast cancer therapy resulted in a significant reduction in the risk of local breast cancer recurrence, leading to a reduction in the risk of mortality. For every four local recurrences avoided by RT in years 1–5, about one death from breast cancer was avoided by year 15 [1]. However, when targeting the breast/chest wall with RT, some radiation is also delivered to the underlying normal tissues (e.g. heart and lung), and RT has been associated with an increased risk of late onset cardiotoxicity and second malignancies. In the EBCTCG analysis there was a significant excess of fatal heart disease (rate ratio 1.27, standard error (SE) 0.07, $P = 0.0001$) among irradiated women. Similarly, an excess incidence of second lung cancer (rate ratio 1.61, SE 0.18, $P = 0.0007$) and lung cancer deaths (rate ratio 1.78, SE 0.22, $P = 0.0004$) was found for irradiated patients. These long term side effects tend to offset the beneficial effect of RT. For example, in the meta-analysis, overall survival remained significantly improved for women given breast conserving surgery and for women with node-positive disease treated with mastectomy and axillary clearance, but for women with node-negative disease treated with mastectomy and axillary clearance, the beneficial effect of RT on breast cancer survival was very small and the toxic side effects outweighed it.

The amount of incidental radiation delivered to the underlying heart is greater with left-sided versus right-sided RT. Similarly, the amount of incidental lung irradiation will generally be greater for the ipsilateral versus contralateral lung. These differences in exposure have been used to evaluate the risk of cardiac disease and second lung cancer associated with RT. Among women diagnosed with breast cancer during 1973–1982 in US SEER cancer registries, an excess cardiac mortality (ratio of 1.42 (1.11–1.82)) for left-side irradiated patients, and excess lung cancer mortality (ratio of 2.00 (1.00–4.00)) for ipsilateral lung cancer at 10–14 years after RT was found [2]. These excess risks increased significantly and progressively with time since RT: cardiac mortality 1.58 (1.29–1.95) and ipsilateral lung cancer mortality 2.71 (1.65–4.48) at 15 years or more after RT.

The risk of late radiation-associated sequelae with modern cancer treatment is uncertain, because older radiotherapy regimens resulted in larger cardiac dose-volume distributions to organs at risk than what is common with modern radiation techniques [3,4]. Nearly all of the above mentioned studies analysed data from an era before the routine use of three-dimensional (3-D) simulation and planning, which allows for more accurate delineation of irradiated heart and lung volumes. Coincident with improvements in RT techniques, there have been observations of decreased incidence of radiation-associated sequelae over time [2,5].

Current research in this area is attempting to define more precisely the risk of radiation-associated sequelae and to deliver RT with improved sparing of organs at risk. A case-control study in Sweden and Denmark, Radiation-Associated Cardiovascular Events (RACE), is estimating irradiated cardiac volumes and correlating estimated cardiac dose with clinical events in an attempt to characterise the cardiac dose-response relationship [6]. Similarly, estimates of the mean ipsilateral lung RT dose have allowed for assessment of second lung cancer risk by RT dose. Two separate studies have reported an estimated increase in the relative risk for second lung cancer of approximately 0.1–0.2 per Gy (mean ipsilateral lung radiation dose) at 10 or more years after RT [7,8].

Other cancer treatment factors may also potentially increase the risk of late sequelae. Chemotherapeutic agents have changed over time, and newer agents such as anthracycline chemotherapy (doxorubicin and epirubicin) and immunotherapy (trastuzumab), which are themselves cardiotoxic, are increasingly being

used. The possible interaction of these drugs and of traditional risk factors for cardiac disease (e.g. age, blood pressure, cholesterol, diabetes, smoking, etc.) with RT remains to be elucidated. There is already evidence for an interaction between smoking and RT on the risk of both second lung cancer and cardiac disease among breast cancer survivors [5,7,9].

There is considerable uncertainty about the extent of risk of radiation associated cardiac disease and second lung cancer following modern treatment methods. However, the prevalence of breast cancer and high long-term survival rates of many breast cancer patients means that even a small risk will result in a substantial number of cases. Reducing irradiation of the heart and lung is feasible for women using, for example, respiratory manoeuvres such as breathing adapted RT [10]. Establishing RT dose constraints for the heart and lung that can be achieved with advances in treatment techniques will hopefully reduce the risk of radiation-associated sequelae for future generations of breast cancer survivors.

Conflict of interest statement

None declared.

Acknowledgement

Funding provided by Cancer Research UK and the UK Department of Health.

References

1 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**366**:2087–106.

2 Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005;**6**:557–65.

3 Taylor CW, Nisbet A, McGale P, Darby SC. Cardiac exposures in breast cancer radiotherapy: 1950s-1990s. *Int J Radiat Oncol Biol Phys* 2007;**69**:1484–95.

4 Taylor CW, Nisbet A, McGale P, et al. Cardiac doses from Swedish breast cancer radiotherapy since the 1950s. *Radiother Oncol* 2009;**90**:127–35.

5 Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007;**99**:365–75.

6 RACE (Radiation Associated Cardiovascular Events), http://race.ki.se/

7 Prochazka M, Hall P, Gagliardi G, et al. Ionizing radiation and tobacco use increases the risk of a subsequent lung carcinoma in women with breast carcinoma: case-only design. *J Clin Oncol* 2005;**23**:7467–74.

8 Inskip PD, Stovall M, Flannery JT. Lung cancer risk and radiation dose among women treated for breast cancer. *J Natl Cancer Inst* 1994;**86**:983–8.

9 Neugut AI, Murray T, Santos J, et al. Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers. *Cancer* 1994;**73**:1615–20.

10 Korreman SS, Pederson AN, Aarup LR, Nøttrup TJ, Specht L, Nyström H. Reduction of cardiac and pulmonary complication probabilities after breathing adapted radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2006;**65**:1375–80.