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Radiotherapy for Breast Cancer: Curing the Cancer While Protecting the Heart

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Radiotherapy has had an important place in the treatment of breast cancer for many years. Since the seminal work of Fisher [1,2] in the 1970s, breast conserving surgery followed by radiotherapy has replaced mastectomy for early stage breast cancer. Locoregional irradiation reduces the recurrence risk and breast cancer mortality both in early stage breast cancer patients following lumpectomy [2] and in patients with more advanced tumors following mastectomy [3]. Nodal irradiation, including internal mammary nodes (IMN), increases survival in high-risk breast cancer [4], with level I evidence of improved cancer specific survival in patients with positive axillary nodes or central and medial tumors [5]. However, radiotherapy to the breast, especially when the IMN are included in the radiotherapy target, risks exposing the heart to radiation [6].

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a meta-analysis of several prospective studies that randomized breast cancer patients undergoing breast conserving surgery to receive or not receive postoperative radiotherapy. The EBCTG publications showed that, although the breast cancer recurrence rate and the mortality rate from breast cancer were reduced following radiotherapy, there was little improvement in overall survival rates due to a parallel increase in non-breast cancer mortality, which was attributed to radiation induced cardiotoxicity (RIC) [7]. The studies on which the EBCTG analysis was based were conducted in the 1970s and 1980s, at a time when there was less awareness of the risk of cardiotoxicity from breast irradiation. Since the 1990s 3-dimensional computed tomography simulation has been routine for the planning of breast radiotherapy allowing individualized blocking of the cardiac outline for left sided disease. Additional techniques, including respiratory gating or prone irradiation, are often used to ensure that for each patient the dose to the heart is kept below what is considered the tolerance dose. These techniques markedly reduce the dose of radiotherapy to the heart and more recent series have consistently shown a reduced incidence of RIC with no statistically significant increase in cardiac related mortality attributable to radiotherapy [8].

Some studies have shown a dose-response relationship between cardiac radiation dose with no demonstrable dose threshold such that even low doses of radiotherapy to the heart may be associated with increased morbidity [9,10]. It is, therefore, imperative to use techniques similar to those described in the article in this issue of *Israel Medical Association Journal* by Kaplinsky and colleagues [11] to reduce the radiotherapy dose to the heart to as low as possible, in particular in the loco-regional treatment of breast cancer patients who are usually cured of their disease and may have a life expectancy of several decades.

Radiation induced cardiotoxicity has received increasing attention in recent years, not only following the radiotherapy of breast cancer but also for patients with thoracic tumors such as Hodgkin's lymphoma and lung cancer. In the case of Hodgkin's lymphoma, radiotherapy delivered to the involved nodes, as seen on initial staging positron emission tomography–computed tomography (PET–CT) (involved node irradiation), is as efficacious as the previously administered mantle field, which has much larger volumes of the heart and lungs, thereby markedly reducing the volume of heart tissue exposed to radiation [12].

Patients in whom the involved mediastinal lymph nodes are in close proximity to the upper cardiac outline can be treated with respiratory gating (using similar techniques as described for breast cancer) to reduce the dose to the heart [13]. In the case of locally advanced (stage III) lung cancer where the treatment of choice with curative intent is often a combination of radiotherapy with chemotherapy, a phase III study showed reduced survival in patients receiving a higher dose of 74 Gy radiotherapy compared to those receiving a lower dose of 60 Gy. This reduced survival has been attributed to higher doses of radiotherapy to the heart leading to increase cardiac related mortality [14]. RIC can manifest itself not only as ischemic events but also as pericardial effusion or cardiac rhythm disorders [15].

Classical radiotherapy fractionation consists of daily doses of 1.8–2.0 Gy in the belief that at these low daily doses there would be limited damage of healthy organs that need to be included in the radiotherapy fields to ensure adequate coverage of the target tumor. We are now aware that even low doses of radiation may risk long-term organ toxicity. The last 30 years have seen the wide use of 3-dimensional imaging to improve radiotherapy planning, including CT, magnetic resonance imaging (MRI), and PET–CT. More recently, 4-dimensional radiotherapy planning combined with image-guidance systems incorporated in the radiotherapy machines have enabled the consideration of tumor and organ movement during treatment and adaptation of the radiotherapy to the breathing cycle. The increased accuracy of advanced imaging techniques has led to lower toxicity allowing the safe delivery of the total radiotherapy dose in larger but fewer daily doses, thereby reducing the overall number of daily treatments and shortening the overall treatment time.

Recent guidelines for radiation therapy of breast cancer, based on several prospective randomized studies, recommend that the standard protocol for whole breast radiation (when no treatment is delivered to the draining lymph nodes) should be reduced to 15 daily fractions (as compared to 25–35 fractions in earlier guidelines) [16]. In women with small tumors of the breast, radiotherapy can be delivered as a short course to partial breast volumes or can even be delivered to the tumor bed at the time of surgery, thereby avoiding any radiation to the heart while further increasing patient convenience.

Image guided techniques to those described in the accompanying study are now regularly used in other tumor sites. For example, in the case of prostate cancer where image-guided radiotherapy has been shown to reduce toxicity compared to conventional radiotherapy, the standard protocol has been shortened from more than 40 treatments delivered in 8 weeks to approximately 30 treatments delivered in 6 weeks with increasing evidence. In many cases, the course of radiotherapy can safely be shortened to 20 treatments in 4 weeks.

Modern radiotherapy requires meticulous attention to detail utilizing all available imaging techniques both for radiotherapy planning and for delivery to achieve the maximum therapeutic benefit from radiotherapy for cancer patients with minimal discomfort and toxicity. The authors of the accompanying study [11] are commended for demonstrating the use of these techniques in reducing the risk of cardiotoxicity in breast cancer patients.

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Capsule

How sleep loss leads to weight gain

Chronic sleep loss can have negative health effects, including weight gain and type 2 diabetes. Underlying molecular processes in key metabolic tissues are thought to be to blame. **Cedernaes** and co-authors compared molecular changes such as DNA methylation in fat and skeletal muscle tissue samples taken from 15 young Caucasian males after a night of sleep loss and after a normal night's sleep. The two tissue types responded very differently. In muscle, sleep loss enhanced skeletal muscle breakdown by down-regulating a metabolic pathway. However, the same pathway was up-regulated in fat tissue after disrupted sleep. Thus, sleep loss may reprogram fat tissue to increase fat storage.

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