Cardiovascular effects of radiation
Fiona Stewart[1], Berthe Aleman[2] and Kiyo Mabuchi[3]

[1]Experimental Therapy and [2]Radiation Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands

[3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Epidemiological data

Radiation-related cardiovascular deaths are not usually seen until 10-15 years after exposure, although non-symptomatic abnormalities may develop much earlier. The long delay before symptomatic expression of damage probably explains why the radiation sensitivity of the heart has previously been underestimated.

The first clear indication of an increased risk of vascular disease after low-dose radiation came from the Japanese atomic bomb survivors enrolled in the Life Span Study (Shimizu et al., 1999; Preston et al., 2003). Individual dose estimates were obtained for >86,000 survivors who received single whole-body exposures in the range 0-4 Gy; mean colon dose 0.15 Gy. In the most recent analysis it was estimated that exposed survivors had an excess risk of death from heart disease of 14% per Gy, relative to unexposed survivors, although for doses of <0.5 Gy the increased risk was not statistically significant. For cerebrovascular disease (stroke) the excess risk of death was 9% per Gy. These estimates were based on a linear dose-response model, which gave the best fit, but for doses <0.5 Gy the degree of risk was uncertain (Shimizu et al., 2010).

Other large cohorts exposed to cardiac or brain doses <5 Gy for treatment of benign disease, or cumulative doses <1 Gy for diagnostic procedures, or whole body occupational and environmental exposures accumulating to <0.5 Sv, were subsequently examined for associations between radiation dose and elevated risk of circulatory disease (reviewed in Little et al., 2008; Little et al., 2010; McGale and Darby, 2005; McGale and Darby, 2008; Metz-Flamant et al, 2009). Some of the individual studies considered in these reviews show a statistically significant increased risk of circulatory diseases in the exposed populations, but others do not. In general, the clearest indications of increased risk are for populations exposed to doses >0.5 Gy and there is a great deal of uncertainty associated with risk estimates at lower doses. An analysis of all relevant epidemiological data on circulatory disease after low radiation doses (heart/brain doses <2.5 Gy and mostly <0.5 Gy) suggested an average excess risk of 8% per Sv relative to unexposed populations. However, there was substantial heterogeneity between the studies and the authors concluded that the epidemiological evidence for increased risk at these low doses was suggestive rather than conclusive (Little et al., 2010). One of the problems in estimating risks at low doses is that cardiovascular disease is known to be markedly influenced by lifestyle factors such as smoking, obesity and stress, which are often unaccounted for in retrospective cohort analyses and may bias the results.

There is a very clear association between high therapeutic doses of thoracic irradiation and increased risks of cardiovascular disease in long-term cancer survivors. This includes a wide spectrum of cardiac pathologies, such as pericarditis, coronary artery disease, myocardial dysfunction, valvular dysfunction and electrical conduction abnormalities. Epidemiological studies on survivors of Hodgkin's lymphoma and childhood cancers show 2 to >7-fold increases in risks for cardiac deaths, depending on the age of the patients (increased risks for irradiation at young age), radiotherapy methods used and the follow-up time (Adams et al., 2004; Aleman et al., 2003; Boivin et al., 1992; Hancock et al., 1993; Swerdlow et al., 2007). In these cases the tumor doses are generally 30-40 Gy, given in a series of daily doses of approximately 2 Gy, although the average dose to the heart may be much less. In a large study of >4,000 long-term survivors of childhood cancer that included individual estimates of cardiac dose, the risk of cardiac mortality among childhood cancer survivors increased linearly with dose. There was an estimated 60% excess risk at 1 Gy, although for analyses restricted to total cardiac doses <5 Gy, there was no significant increased risk (Tukenova et al., 2010). These dose calculations do not include any adjustment for the fractionated dose delivery, which is biologically less damaging than a single exposure (Schultz-Hector and Trott, 2007).

Increased cardiac morbidity and mortality has also been widely reported after treatment for breast cancer (Adams et al., 2003; Gaya and Ashford 2005; Senkus-Konefka and Jassem, 2007). The excess risks are lower than for Hodgkin's lymphoma and childhood cancer patients but the large numbers of women involved means this is a significant health concern. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) evaluated individual patient data from >30,000 women in randomized trials of radiotherapy versus no radiotherapy (Clarke et al., 2005). This study showed a 27% excess of heart disease in the irradiated group. The risk of cardiac death was related to the estimated mean cardiac dose, increasing by 3 % per Gy without adjustment for fractionation effects (Darby et al. 2010).

Experimental data and mechanisms of damage
The endothelial cells lining blood vessels are sensitive to radiation. Experimental animal studies have shown that radiation doses $\geq$ 2 Gy induce expression of inflammatory and adhesion molecules (as discussed in Schultz-Hector and Trott, 2007; Little et al., 2008). When combined with elevated cholesterol levels, this both initiates and enhances atherosclerotic development in irradiated arteries. It also predisposes to the formation of unstable lesions, which are prone to rupture and may cause a fatal heart attack or stroke (Vos et al., 1983; Tribble et al., 1999; Pakala et al., 2003; Stewart et al., 2006; Hoving et al., 2008). Localized changes in the irradiated arteries, rather than systemic changes were responsible for the effects seen in these studies. Major arteries such as coronary and carotid arteries are the most susceptible to atherosclerotic plaque formation, especially at bifurcations (branching sites).

In contrast to the inflammatory processes initiated by localized irradiation with doses > 2 Gy, whole body doses of 0.1- 0.6 Gy have been shown to inhibit inflammatory cell adhesion to endothelial cells (Arenas et al., 2006) and doses of $\leq$0.05 Gy exerted some protective effects on the development of atherosclerosis in mice, particularly at low dose

rates (Mitchel et al., 2011). This suggests a non-liner dose response relationship for radiation induced atherosclerosis, which may be relevant to some epidemiological observations of a protective cardiovascular effect from very low dose occupational exposures (0.02 Sv), but detrimental effects at higher doses (0.2 Sv) (Vrijheid et al., 2007).

In the heart, radiation-induced damage to the myocardium is primarily caused by damage to the microvasculature, leading to inflammatory and thrombotic changes, capillary loss, focal ischemia and interstitial fibrosis after high doses (reviewed in Adams et al., 2003; Schultz-Hector and Trott, 2007). The inflammatory changes in capillary endothelial cells, lead to adhesion of circulating lymphocytes, which then invade the capillaries and cause thrombi formation and obstruction of the microvessels. Progressive reduction in the number of patent capillaries eventually leads to reduced perfusion of the cardiac muscle, ischemia, myocardial cell death and fibrosis (Fajardo et al. 2001; Schultz-Hector, 1992). Myocardial degeneration coincides with the first signs of decreased cardiac function in rats. However, further decreases in function do not occur until shortly before the onset of fatal congestive heart failure, despite increasing degeneration of myocardial mass (Schultz-Hector, 1992). This is probably explained by compensatory mechanisms masking the extent of functional damage. The animal data are supported by clinical studies that demonstrate regional perfusion defects in non-symptomatic breast cancer patients at 6 months to 5 years after radiotherapy (Gyenes et al., 1996; Marks et al., 2005; Seddon et al., 2002).

Microvascular damage and accelerated atherosclerosis, as described above, are the likely underlying causes of radiation-induced cardiovascular damage after medium to high doses to the whole or part of the heart, such as after radiotherapy to the thorax. However, it seems likely that other mechanisms are responsible for cardiovascular effects after whole body exposures at much lower doses. Persistent increases in pro-inflammatory cytokines and long-term impairment of T-cell-mediated immunity, as seen in atomic bomb survivors (Hayashi et al., 2003; Kusunoki et al., 1999), may well be involved. It has also been postulated that radiation-induced genomic instability (Schultz-Hector and Trott, 2007), or monocyte killing and increased levels of the chemoattractant proteins (Little et al., 2010) may play a role in initiation and progression of atherosclerosis after low doses.

Modulation of radiation effect
There are no known specific mitigators of radiation-induced cardiovascular disease. Possibilities are statins, used generally to treat heart conditions, glutamine supplementation, and laboratory research is further investigating the benefits of using stem cell transplantation or stem cell products. Currently, people at increased risk of radiation induced cardiovascular damage are recommended to limit known risk factors for cardiovascular diseases as much as possible.

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