Biological mechanisms of radiation-induced cardiovascular disease

Prof. Fiona Stewart
The Netherlands Cancer Institute, Amsterdam

Epidemiological studies have shown a clear association between high therapeutic doses of thoracic irradiation and increased risks of cardiovascular disease in long-term cancer survivors, although these effects may take decades to become symptomatic. Survivors of Hodgkin’s lymphoma and childhood cancers have 2 to >7-fold increased risks for cardiac deaths after total tumour doses of 30-40 Gy, given in 2-Gy fractions. Increased cardiac morbidity and mortality has also been widely reported after irradiation for breast cancer. Only a small part of the heart is included the treatment fields for breast cancer and the risks are consequently lower than for Hodgkin’s lymphoma survivors (RR 1.1-1.4). Some studies also show increased risks after much lower total body radiation exposures. A-bomb survivors, for example have estimated excess risks of death from heart disease and cerebrovascular disease of 14% per Gy and 9% per Gy, respectively.

The mechanisms whereby these effects occur are not fully understood and it is likely that different mechanisms are involved after high doses to the heart, or part of the heart, than after low total body exposures. It is also likely that these various mechanisms result in different cardiac pathologies, e.g. coronary artery atherosclerosis leading to myocardial infarct versus microvascular damage and fibrosis leading to congestive heart failure. Experimental studies can help to unravel some of these mechanisms and may identify suitable strategies for managing these risks. Experimental studies show that doses ≥ 2 Gy induce the expression of inflammatory and thrombotic molecules in endothelial cells. In the heart this causes progressive loss of capillaries and reduced angiogenic responses, and eventually leads to reduced perfusion, myocardial cell death and fibrosis. The animal data are supported by clinical studies demonstrating regional perfusion defects in non-symptomatic breast cancer patients 6 months after radiotherapy. Local irradiation of large arteries with doses ≥ 2 Gy, in combination with elevated cholesterol, initiates and accelerates the development of atherosclerosis. It also predisposes to the formation of unstable lesions, which are prone to rupture and may cause a fatal heart attack or stroke. By contrast, there is experimental evidence that local inflammatory processes and atherosclerosis may be inhibited by doses of <0.5 Gy. It therefore seems likely that mechanisms other than atherosclerosis are responsible for increased risk of cardiovascular damage after low total body exposures to irradiation. Systemic increases in pro-inflammatory cytokines and long-term impairment of T-cell-mediated immunity (T-cell senescence) may well be involved. There is also some evidence that low-dose cardiovascular effects are, at least partly, secondary to increased serum cholesterol levels and renal damage after total body exposures.

In this overview, the main epidemiological and clinical evidence for radiation-induced CVD will be summarised. Experimental data shedding light on some of the underlying pathologies and possible targets for intervention will also be discussed.
CURRICULUM VITAE

Fiona Anne Stewart:

Born: 27th April 1952, Wakefield, Yorkshire, UK

Degrees:  BSc Biology, London University (1973); PhD Radiation Biology, London University (1978)

Professional Appointments:  Post-doc, Gray Laboratory, Northwood, UK (‘78–’84); Senior Post-doc, the Netherlands Cancer Institute, Amsterdam (NKI) (‘84–’88); Assistant Professor NKI (‘88–’96); Associate Professor NKI (‘97- present).

Board Membership of professional bodies:  Netherlands Radiobiology Society (‘92–’04); Netherlands Medical Laser Society (‘97–’03); Secretary Treasurer International Association Radiation Research (‘99–’08); International Commission for Radiological Protection (ICRP) (‘00–’13); Chair ICRP Task group on Radiation Tissue Effects (‘05–’12); Councillor Radiation Research Society (‘02–’05); Chair Radiation Research Education Committee (‘03–’07); ESTRO Education Committee Core member (‘03–’10); NVRO scientific committee (‘06–’12); ESTRO Radiobiology Committee (‘07–’13); ESTRO Board (‘10–’13); Scientific Advisory Board EU 7th framework PROCARDIO (‘11–’13).

Editorial Board Member:  Radiation Research (‘00–’04); International Journal Radiation Biology Oncology Physics (‘00–’10); International Journal Radiation Biology (‘09–’10); Radiation Research Senior Editor (‘11–’13).

ESTRO teaching activities:  Organized courses in:  Den Haag (‘88), Prague (‘02), Leipzig (‘06); Basic Clinical Radiobiology (‘93–’02), Northwood UK (‘93), Amsterdam (‘04), Istanbul (‘00)

Other teaching activities:  Belgian Society for Radiotherapeutic Oncology (‘84, ’07–’13); Egyptian Radiation Oncology Society (‘90); Swedish Radiation Oncology Society (‘96, ’00); NVRO Dutch Radiobiology courses (‘99–’13); Dutch undergraduate medical students (‘04–’06); Oncology Research Amsterdam (‘05–’12); European School of Oncology, Milan (‘04, ‘05); American Radiation Research Society, organized pre-meeting workshops (‘04–’06); FRCR Manchester, UK course (‘07–’12); Oxford MSc course (‘10–’13); Vancouver Radiation Oncology residents (‘10).

Research interests:
The main focus of my lab is radiation induced endothelial cell and vascular damage in the development of late normal tissue injury. The aim of our studies is to investigate mechanisms underlying the development and progression of radiation-induced vascular damage, with a view to identifying and testing intervention strategies. Ongoing projects use endothelial cells in culture, mouse models and biopsies of irradiated and control tissue from cancer patients, to study how radiation induces inflammatory and thrombotic changes in capillaries and large vessels and how these changes lead to progressive development of tissue damage and to atherosclerosis.

This research has resulted in >150 peer reviewed scientific publications

Honours and Awards:
Association for Radiation Research Weiss Medal Award 2012
Publications in last 5 years (from a total of >150)


