Editorial

Radiotherapy, left-sided breast cancer, and ischaemic heart disease

Postoperative radiotherapy is an established treatment to improve local and regional control of breast cancer. However, three large studies in which early disease was treated by mastectomy and radiotherapy failed to show improved survival.¹⁻³ They all showed a significant increase in cardiac death after radiotherapy which was greater for left-sided disease. Radiotherapy as a cause of coronary atherosclerosis is suggested by several small studies and case reports of ischaemic heart disease after mediastinal radiotherapy mainly for Hodgkin's disease.⁴⁻¹² Here we consider the evidence that radiotherapy for left-sided breast cancer induces coronary atherosclerosis and subsequent cardiac mortality and morbidity. This has important implications for radiotherapy treatment techniques and the follow up and perhaps treatment of patients with early breast cancer.

Cardiac death after radiotherapy for early breast cancer

Three large studies investigated the cause of death after radiotherapy for early breast cancer.¹⁻³ These focused on early disease because long-term survival is common so that iatrogenic morbidity and mortality may be as important as the underlying disease process. In the Cancer Research Campaign trial 2800 patients with stage I or II carcinoma of the breast were prospectively randomised to simple mastectomy with or without postoperative radiotherapy.¹ The treatment period was 1970-1975 with up to 19 years follow up. There was no significant difference in the overall death rate but in the radiotherapy group mortality from causes other than breast cancer was significantly increased (relative risk 1.37 (95% confidence interval, 1.09 to 1.72)). This was most pronounced for those with left-sided tumours, especially those treated by an orthovoltage technique. The relative risk of cardiac death after 5 years in these patients was 2.67 (95% CI, 1.28 to 5.55). The difference between left and right did not achieve statistical significance.

In the Manchester Study 1461 patients were prospectively randomised between 1949 and 1955 to radical mastectomy alone or with postoperative radiotherapy.² There was an excess mortality in the radiotherapy group with excess deaths caused by cardiovascular (non-cerebrovascular) causes after 15 years (relative risk 1.43 (95% CI, 1.13 to 1.81)). The risk was greatest for left-sided tumours but a test for an interaction effect was not significant.

In the Oslo study 1115 patients received radical mastectomy alone or with postoperative radiotherapy between 1964 and 1972 (11-20 years follow up).³ There was a significant excess mortality in one cohort of the irradiated group (those receiving lymph node irradiation by cobalt-60) due to myocardial infarction. There was a non-significant trend for the excess to be greater with left-sided tumours.

Thus there is evidence from three large studies that in selected groups of patients radiotherapy given after mastectomy for early breast cancer by the techniques in use between 1949-1975 may have reduced survival by inducing late cardiac death. Though it was not significant, there was a trend in all the studies for those patients receiving radiotherapy for left-sided tumours to have a

greater increase in mortality. These trials used outdated surgical and radiotherapy techniques but have the necessary long-term follow up. In addition they only studied mortality and not additional morbidity as an end point.

Radiation induced heart disease

The first cases of radiation associated myocardial infarction were reported in 1957.⁴ Subsequently, several short series were presented.⁵⁻¹² Importantly, the patients had few conventional risk factors for coronary artery disease and atypical sites of atherosclerosis. When McEniery *et al* reviewed the angiograms in their patients they identified 15 patients with coronary artery disease after chest radiotherapy. The mean (SD) dose received was 41(7) Gy 16(8) years before and there was a high incidence of lesions of the left main stem coronary artery and ostial lesions of the right coronary artery in relatively young patients with few conventional risk factors. Applefeld *et al* identified six patients with coronary artery disease among 48 investigated after mediastinal radiotherapy for Hodgkin's disease.⁶ The mean follow up was eight years and the approximate mean dose 40 Gy. Radwaner *et al* reported the case of a 27 year old woman with no conventional risk factors who presented with a tight ostial left main stenosis 8 years after mediastinal radiation (46 Gy).⁷ A similar case of a 12 year old boy presenting 6 years after mediastinal radiation (29 Gy) was reported by Totterman *et al*.⁸ Gustavsson *et al* found two abnormal myocardial scintigrams in 23 patients irradiated for Hodgkin's disease more than 10-20 years previously.¹⁰ A further 10 studies showed uneven uptake which might represent ischaemia but coronary angiography was not performed on these patients. In other reports percutaneous transluminal coronary angioplasty¹¹ and coronary artery bypass grafting¹² were used to treat coronary artery disease after mediastinal radiotherapy. Radiation associated atherosclerosis has also been described in the carotid¹³ and cerebral vessels.¹⁴

In an experimental rabbit model Amromin *et al* showed synergism between radiation and hypercholesterolaemia in producing coronary atherosclerosis.¹⁵ In dogs radiation produced intimal proliferation in the coronary arteries.¹⁶ However, no long-term studies have been performed in animals. Some human data also suggest a different pathological mechanism with intimal fibrous thickening and adventitial scarring of the coronary arteries at necropsy.⁹ Thus there is good evidence that therapeutic radiation can induce late atherosclerosis though the mechanism is uncertain. Radiotherapy for breast cancer uses techniques that are different from those for mediastinal irradiation and the cardiac dose is often not calculated. The newer megavoltage techniques have significantly reduced the cardiac volume irradiated but a segment of the anterior wall still receives a dose of approximately 50 Gy which is similar to the breast target dose.¹⁷ This territory includes part of the left anterior descending artery, with the other major vessels receiving a much smaller dose. Atherosclerosis of this vessel probably has more serious consequences than that of other vessels.

Conclusion

Evidence supports the proposal that the excess cardiac mortality reported after radiotherapy as practised in the 1950s–1970s for early breast cancer, particularly left-sided, was due to radiation-induced coronary atherosclerosis. This may have led to myocardial infarction and death and also to ischaemia induced cardiac morbidity.

Modern radiotherapy techniques have reduced the total cardiac dose but they still irradiate a segment of the left anterior descending coronary artery. The significance of this remains to be confirmed by prospective studies. The evidence presented suggests that the radiation dose to the anterior left ventricular wall should be minimised and the known risk factors for coronary artery disease, particularly hypercholesterolaemia, reduced. Additionally, cardiological sequelae in patients surviving more than 5 years should be considered. In the series discussed patients presented with angina pectoris^{5–11} so a careful history of chest pain should be sought. Treatment with low dose aspirin after radiotherapy for left-sided breast cancer should be debated.

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