Evidence of circulatory diseases among patients treated with radiotherapy

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Radiotherapists have known for a long time that blood vessels in the high dose volume of radiotherapy may after latencies of many years, develop atherosclerosis and cause thrombotic events. Radiation-induced thrombosis of the carotid arteries and subsequent stroke has been the most commonly reported late circulatory disease after radiotherapy of head and neck cancer. A recent report by Dorresteijn (2001) described the clinical experience of a cohort of 367 patients treated with radiotherapy for head and neck cancer at the National Cancer Institute in Amsterdam**.** Fourteen cases of stroke occurred between 1 and 20 years later. The mean latency was 10 years. In this relatively young population with a mean age of 63 years at the time of the stroke, the rate of ischaemic stroke was significantly increased by more than a factor of 5, compared to an age matched normal population. In those patients who were followed for more than 10 years, the risk of stroke was even ten times higher than in the general population! Thus, there appeared to be good epidemiological evidence that exposure of major arteries to high radiation doses is an independent risk factor in human vascular disease.

Yet the situation is not as simple as it may appear from the Amsterdam data**.** A few weeks ago, at the annual meeting of the American Society for Therapeutic Radiology and Oncology, abstract #89 by Huang et al. (2008) described the results of the largest epidemiological analysis yet of the rate of strokes after radiotherapy of head and neck cancer. This study was based on about 100.000 eligible patients with head and neck cancer documented in the Surveillance, Epidemiology, and End Results (SEER) cancer registry data base which covers approximately 10 % of all US cancer patients. Nearly 10,000 of those patients were hospitalised within 10 years after cancer treatment because they suffered a stroke. 10% of the patients who were treated with radiotherapy developed a stroke compared to 7.5% of the patients who were treated surgically. This is an increases by 33%, still a large increase but nowhere near the 500% identified in the Amsterdam study. This dramatic difference of the results from the Amsterdam study and the recent SEER study can probably be attributed to the fact that patients who develop head and neck cancer generally also have a

very high risk of developing a stroke. This would be expected from their particular life style which favours the development of both, head and neck cancer and stroke, alike, as both share major risk factors such as excessive alcohol consumption, smoking and others.

One of the most comprehensive, critical reviews of the older clinical data has been published by Schultz-Hector in 1995. It is based on nearly 100 clinical reports, most of which are concerned with high dose exposure to the carotid or to the coronary arteries. These arteries frequently develop atherosclerotic changes spontaneously, but they are also often exposed to doses between 40Gy and 70Gy in the treatment of common cancers such as head and neck cancer, breast cancer and lymphomas. More informative than the clinical diagnosis of stroke are the results of non-invasive imaging investigations in those patients which revealed a rate of approximately 25% of significant stenosis of the carotid arteries. A report from Nijmegen (Dorrestijn et al., 2005) demonstrated that the thickness of the irradiated arterial walls progressively increased during the follow-up period.

For our discussion today, the most important result of the review by Dr. Schultz-Hector is the dose response relationship which she drew from the collected data and which was based on the prescribed dose in head and neck cancer patients (figure 1)**.** The dose dependence of severe stenosis rate at doses >40 Gy is proof of causality. Yet the high base rate and the frequent and variable exposure of people to known other risk factors makes any extrapolation to low radiation dose levels very uncertain.

Also the findings from non-invasive imaging investigations support the important role of radiation exposure for the development of atherosclerotic changes. The radiation-induced atheroma plaques nearly always occur throughout the very high dose volume which received the target dose, i.e. the same dose as the treated cancer. On the other hand, the spontaneous stenosis of the unirradiated patients nearly always is restricted to the bifurcation.

In addition to the carotid artery, radiation-induced atherosclerosis has also been described for the coronary arteries in the heart. The most convincing evidence for a role of radiation exposure in its pathogenesis, besides the well known metabolic and dietary factors, comes from those patients who developed coronary heart disease at a very young age. Coronary heart disease below the age of 41 is very rare unless several strong risk factors are present. Yet Dr. Schultz-Hector found reports on more than 40 patients who developed coronary heart disease at this young age who had received radiotherapy which included part of the heart but who did not present with the usual risk factors.

The latency until the manifestation of the radiotherapy-associated atherosclerosis which becomes manifest as stenosis can be very long. Even 10 years after radiotherapy with high radiation doses, no more than half of the stenosis have become clinically manifest.

Whether radiation-induced stenosis of the major arteries such as carotids leading to stroke, or of the coronary arteries leading to myocardial infarction are indeed a problem radiation protection needs to be concerned with, cannot be answered from these radiotherapy data, despite the fact that the A-bomb survivor data suggest a linear dose dependence of stroke at doses more than one order of magnitude lower than those reported by the radiotherapists. It is for this reason that the CARDIORISK project included this problem in its work-programme. Yet, there can be no doubt that this problem is bound to become a serious issue in modern radiotherapy. New techniques in clinical radiotherapy, in particular stereotactic radiotherapy require careful re-consideration of radiation doses to the major blood vessels (Nieder et al. 2006)

The clinical importance of radiation-induced heart disease was recognised later. Initially it was mainly related to radiotherapy of Hodgkin's disease. Based on the follow-up studies in Hodgkin's disease patients, it was concluded that radiation-induced heart disease may assume three different clinical manifestations which is pericarditis, myocardial insufficiency and ischaemic heart disease. These different clinical manifestations have different latency distributions and, also show different dependency on dose-volume relations. (Table 1) In recent years, the high rate of ischaemic heart disease in Hodgkin's patients which usually occur more than 10 years after radiotherapy has attracted particular attention. The Amsterdam cohort study on more than 1200 Hodgkin's disease patients by Aleman (2003) is a good example of such a study (Table 2)**.** The most important message is that despite the large numbers of radiation-induced heart failure and a similar number of radiation-induced second cancers, the main problem remains the failure to control the primary cancer. With very few exceptions, this is the message of most studies on cardiovascular risk in radiotherapy patients: the main risk after radiotherapy is recurrence of the treated cancer.

The classical treatment fields as introduced half a century ago by Kaplan in Stanford and Musshoff in Freiburg for mediastinal Hodgkin's disease (the mantle field) leads to doses of up to 40 Gy in large parts of the heart. Vordermark et al (2006) was among the first to use modern treatment planning methods to reconstruct, in retrospective, dose distributions in Hodgkin's patients many years after treatment in order to relate findings of functional imaging of the hearts of irradiated patients to those dose distributions. The results of the functional imaging investigations cause concern, in particular the unexpected high frequency

of vascular, mostly microvascular perfusion changes. Modern radiotherapy of Hodgkin´s disease is very different, with more emphasis on chemotherapy and on giving lower radiation doses to smaller volumes, i.e. those which are clinically involved by malignant disease. No studies have been presented on the results of functional imaging in patients who were treated more recently with the new protocols.

It is only since the early nineties that the heart as been found to be a critical organ in other areas of radiotherapy and in radiation protection. The observations made since the early 1990s of a significant dose dependent increase in cardiovascular mortality among the Life Span Study cohort of the Japanese A-bomb survivors (latest up-date by Preston et al., 2003) stimulated a number of studies in radiotherapy patients. The Stockholm group reported the first convincing evidence that, compared to breast cancer patients treated by surgery alone, breast cancer patients treated with post-operative radiotherapy revealed a dramatic increase in mortality from ischaemic heart disease. (Rutqvist et al 1992). This finding initiated a large number of more studies into the cardiovascular radiation risks associated with post-operative radiotherapy of breast cancer patients. The same group in Stockholm also published the first study into the pattern of blood perfusion in hearts of breast cancer patients treated with radiotherapy. They reported that about 50% of the patients had new scintigraphic defects which they related to radiation damage to the micro-circulation (Gyenes et al., 1996).

Despite these reports in the early nineties of the last century, it is only very recently that radiotherapy-associated cardiovascular disease has been recognised by radiation oncologists as a significant clinical problem. The first time that radiotherapy-induced heart disease was given a special symposium at an international meeting of radiation oncology was only two years ago at the German Congress of Therapeutic Radiology and Oncology in Dresden. However, the awareness of the seriousness of this problem has spread rapidly. This is documented for example by the fact that at the recent meeting of the American Society of Therapeutic Radiology and Oncology (ASTRO) as many as 22 presentations dealt with radiation exposure and radiation risk of the heart in radiotherapy.

This sudden interest of the radiotherapy community in very late occurring radiation damage to the heart was stimulated by two major reports on the increase of the rate of myocardial infarctions and other ischaemic heart diseases after post-operative radiotherapy of breast cancer. In these patients, part of the heart is exposed to the target dose of 40 to 50 Gy, while the mean organ dose usually is only a few Gy given in very small fractions. After correction for fractionation effects using the linear quadratic model and the α/β ratio determined in experimental studies in the rat heart of 1 – 3 Gy, equivalent single doses to the

total heart are about 1 – 2 Gy and thus very similar to the heart doses in the A-bomb survivors who developed fatal radiation-induced heart disease (Schultz-Hector and Trott, 2007).

The Surveillance, Epidemiology and End Results cancer registry data base provide unrivalled opportunities to study the effects of radiotherapy on radiation-induced cardiovascular diseases. They have repeatedly been analysed. Probably the first to compare the risk from radiotherapy according to whether the breast cancer had affected the left or the right breast was Paszat et al. in 1998. Also using the SEER data, the Oxford group of Darby et al. (2005) demonstrated the most significant evidence that the risk continuously increased with time after radiotherapy (Table 3)**.** In the total cohort of more than 300.000 women who are recorded in this data base as being treated for early breast cancer between 1973 and 2001, about 115.000 received post-operative radiotherapy as part of the primary treatment. Of those 4.130 women who died more than 10 years after radiotherapy, 1.721, that is 42 % died from recurrent breast cancer, but 894, that is 22%, half as many as from recurrent cancer, died from heart disease. Whereas the risk of death from recurrent breast cancer was the same after left- or right-sided cancer, the risk of death from heart disease was higher by 44% in those women who had cancer of the left breast than in those women who had cancer of the right breast. In absolute numbers, 359 women with right-sided breast cancer and 535 women with left-sided breast cancer died from heart disease. This is an excess of 176 deaths of which 44 are due to myocardial infarction and 72 from other ischaemic heart disease. All of this excess of fatal heart disease has to be attributed to the higher radiation dose to the heart in patients with left-sided breast cancer. In the 1970s, the mean heart dose for right-sided breast cancer from the tangential fields was in the order of 5 Gy, but for left-sided breast cancer this was about 10 Gy. The 5 Gy higher dose, given in fractions of <0.25Gy, after correction for fractionation is equivalent to an additional single dose of about 1.5Gy which could be regarded as the cause of the increased risk of cardiovascular death by 44%. In this study design, each patient was her own control - no other epidemiological protocol can provide such perfect control. The excess risk is not significant in the first 10 years after treatment but its significance and its magnitude increases progressively with follow-up time.

Because both surgical and radiotherapy procedures changed dramatically over the analysed period of time, the two decades between 1973 and 1982 and between 1983 and 1992 were also analysed separately. Confidence limits for the later period are large, but there is little evidence that the advances in radiotherapy techniques decreased the excess relative risk of radiation-induced heart disease significantly.

The second large data base used to investigate the risk of fatal radiation-induced heart disease after radiotherapy of breast cancer is that of the Early Breast Cancer Trialists´ Collaborative Group (EBCCG). This data base is particularly valuable as it is based on a large number of randomised clinical trials. The analysis of the cause specific mortality among 20.000 women at 10 to 20 years after primary treatment for breast cancer clearly demonstrated the superb effectiveness of adjuvant radiotherapy not only to reduce the risk of loco-regional treatment failure from 30% to 10%, i.e. by a factor of 3. (Table 4) Also the risk of death from breast cancer, including death from distant metastasis was significantly reduced. However, this clinical benefit relating to death from cancer did not translate into any survival benefit because it was offset by a statistically significant increase of deaths from cardiovascular disease. These have to be ascribed to inadvertent irradiation of the coronary arteries, the carotid arteries and the micro-vasculature of the heart.

Also single institution studies such as those performed in the Netherlands Cancer Institute by Hooning et al.(2006 and 2007) provided important additional information, in particular with regard to treatment details. Whereas post-operative radiotherapy after mastectomy increased the risk of cardiovascular death two-fold, no increase was observed after post-operative radiotherapy when the surgical procedure was breast conserving surgery. This difference may be ascribed to different radiotherapy techniques leading to different dose volume relationships. Yet, a later study by the same group (Borger et al., 2007) did not find a significant influence of irradiated heart volume on cardiovascular radiation risk. It is becoming increasingly clear that although the large studies such as the SEER studies and the EBCCG studies were crucial in identifying and quantifying the importance of the problem, they cannot help solving the problem. The key problem of which anatomical structures are important for the risk and define dose response relationship can best be investigated in smaller but more detailed studies. The most important of those studies is the Radiation Associated Cardiovascular Events study, the RACE study.

Also radiotherapy of non-malignant disease has been shown to be a significant cause of radiation-induced heart disease. (Carr et al., 2005; Table 5) Between 1936 and 1965, nearly 1500 patients, suffering from peptic ulcer received fractionated radiotherapy to the stomach with a total dose between 9 and 18 Gy to reduce gastric secretion of hydrochloric acid. A similar number of patients suffering from the same disease but treated with drugs were selected as control group. After a latency of >10 years, mortality from coronary heart disease was significantly increased in the radiation group by 24 %. Moreover, a significant

relationship between the mean heart dose and the relative risk of mortality from coronary heart disease was calculated.

In all radiotherapy studies and scenarios, there is pronounced heterogeneity of doses within the heart. It has been demonstrated already by the Stockholm group ten years ago that dose and volume appear to be important parameters defining cardiovascular radiation risk (Gyenes et al., 1998). As a first approximation we compared the results of the different studies, including the A-bomb survivor studies, by relating the reported relative risk of cardiovascular mortality to the estimated mean heart dose, but correcting the given dose for fractionation using the linear quadratic model which is the generally established standard procedure in clinical radiation oncology**.** (Figure 2) Despite the great differences in dose distribution between all studies, the results of all studies fit surprisingly well to a common dose response relationship if the LQ-corrected mean heart dose is used as denominator of dose. This does, however, by no means prove that the mean heart dose is the relevant criterion for the estimation of cardiovascular radiation risks.

Current and planned research on radiation-induced cardiovascular disease in radiotherapy patients, particularly in the RACE project, concentrates on the relationship between local dose and risk, i.e. the determination of the dose at the site of damage development and thus the identification of the anatomical structures which are the targets that trigger damage development. Closely related is the question how the heart dose is to be reported and limited or constrained in radiotherapy and in radiation protection. Is it the mean heart dose, or the maximum heart dose, or the dose in particular anatomical structures of the heart, such as the left anterior descending coronary artery which in most cases receives the highest radiation dose in radiotherapy of breast cancer? This is presently the most important issue in research on cardiovascular radiation risks, particularly in radiotherapy.

The RACE study (www.race.ki.se) is a large case control and a case/case study on those breast cancer patients from the Danish and the Swedish cancer registries who later developed severe heart diseases. Through linkage of cancer registry data and hospital discharge codings, many hundred women were identified who developed myocardial infarctions and other ischaemic heart diseases after being cured from breast cancer. The case control study with 1000 cases and 1000 controls, i.e.matched breast cancer cases but without heart disease, aims at identifying mainly the radiation dose relationship of cardiovascular risk. In contrast, the case/case study concentrates on the relationship between the localisation of the myocardial infarction or of the ischaemic lesion, and the anatomical dose distribution in the

heart in the individual patient in order to define the target for dose definition and to suggest underlying mechanisms..

These aims of the RACE study require enormous effort to reconstruct, from stored treatment plans, the individual anatomical dose distributions. Several publications on this aspect of the problems by the RACE project, one published (Taylor et al, 2007), others submitted demonstrate that this is difficult but possible.

The individual mean heart doses and the doses for each of the three coronary arteries were estimated based on the individual stored radiotherapy charts which often also included photographs of the treatment fields and drawings of the actual dose plans. These individual doses will form the basis of the on-going case control study. A wide range of doses to the heart and the three coronary arteries were determined**.** (Table 6) The greatest source of variability in cardiac dose estimation for any particular treatment plan was found to be the effect of differing patient anatomy, e.g. heart position in relation to breast, body fat and shape of the thorax. Nevertheless, the difference in heart dose produced by anatomical variation was smaller than the difference produced by different radiotherapy regimes. Calculated mean heart doses changed very much over time. They were highest in the seventies and have continuously fallen since and continue to do so. This is due to changes in target definition, changes in treatment technique, and probably mostly due to growing awareness of the potential problem of radiation-induced heart disease for breast cancer patients, most of whom have a mean life expectancy of more than 20 years after cure, long enough to experience the clinical manifestation of their radiation risk.

The scientists working in the RACE project are confident that the wide range of coronary artery doses, as well as mean heart doses, with detailed information on morbidity and mortality from heart disease in the RACE study should provide solid clinical and dosimetric data for the development of reliable dose response relationships for several cardiac endpoints and several cardiac structures. These results are expected to enable the prediction of future cardiac risks associated with current and evolving radiotherapy regimens.

This approach is a model for future research into other normal tissue damage probabilities and also on second cancer risk in current and emerging treatment modalities in radiation oncology which is the main aim of the new ALLEGRO project which will start early next year.

Future clinical studies in radiotherapy patients could link the results of the mouse studies with the results of the epidemiological studies. The most promising approach are

clinical studies based on modern non-invasive imaging procedures such as SPECT, PET and CT/PET.

Some recent studies using SPECT or PET imaging of micro-vascular perfusion demonstrated perfusion defects already within 6 - 12 months after breast cancer radiotherapy**.** (Table 7) More clinical studies are in preparation with the aim of relating those changes in functional imaging and their gradual development to the individual dose distribution.

Research in the field of cardiovascular radiation risks in radiotherapy has to integrate, as much as possible, clinical and epidemiological research with experimental studies in vivo and in vitro to analyse and to answer the critical open questions**:**

1. Is there a dose threshold of increased risk? Does the latency to clinical manifestation depend on dose as is suggested by experimental data? In other words? Is there a dose dependence of incidence or rather a dose dependence of damage progression rate?
2. What is the clinical nature of cardiovascular disease induced by different radiation doses and dose distributions to the heart? Is the pathology after low radiation doses different, or the same but developing more slowly, compared to that after high radiation doses?
3. In the radiotherapy studies, there are pronounced dose inhomogeneities within the heart. Which part of the heart is most radiosensitive and should be chosen as a reference point for tolerance doses in radiation oncology or for effective dose to be corrected with an organ weighting factor in radiation protection?

The current CARDIORISK project aims at addressing some of these questions experimentally in mice after local heart irradiation.

I conclude that clinical, epidemiological and functional imaging studies in radiotherapy patients have great potential to provide some essential evidence which could help to assess vascular and, in particular, cardiovascular radiation risks not only in radiation oncology but also after exposure to intermediate and to low radiation doses in radiation protection..

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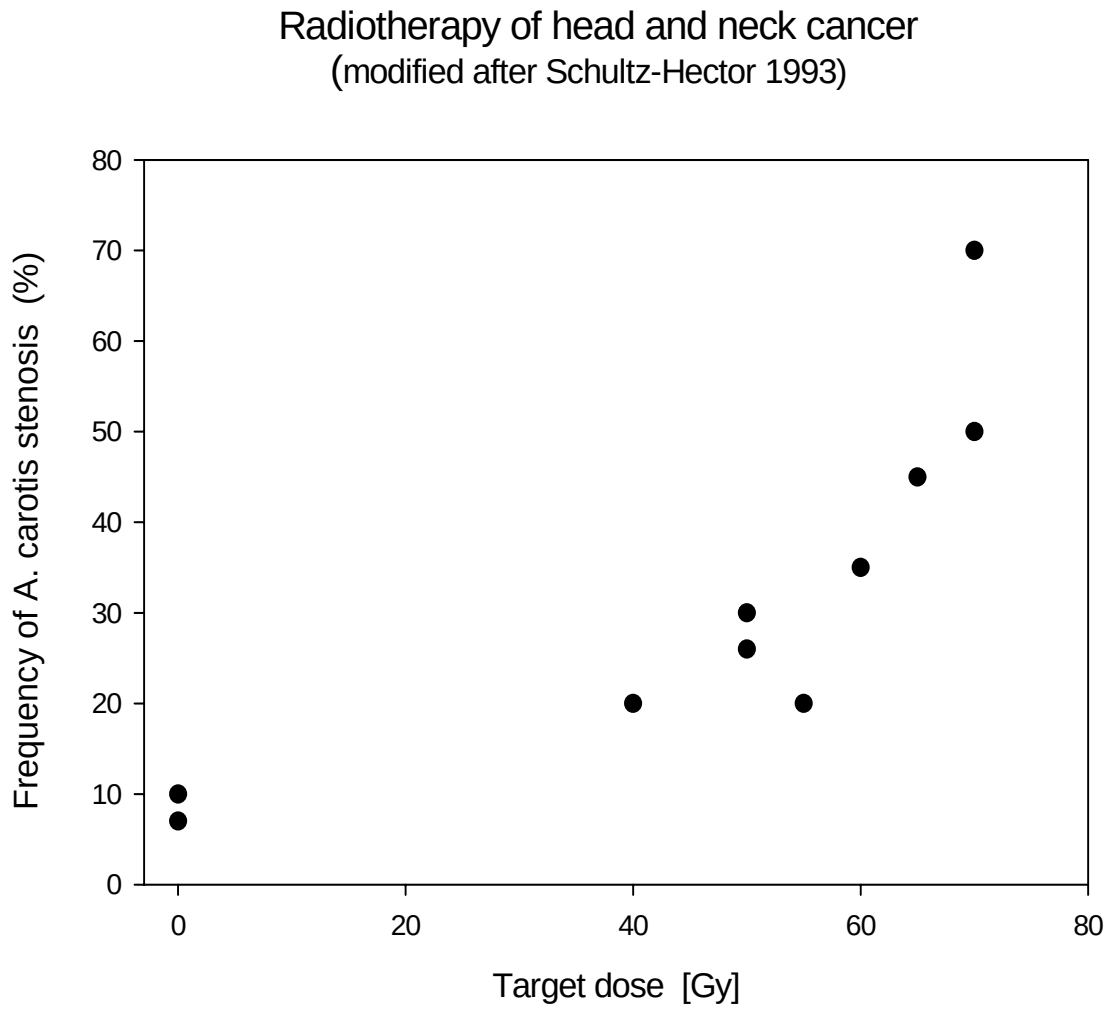

Figure 1: The dependence of the frequency of stenosis of the arteria carotis after radiotherapy for head and neck cancer. Each point represents the result of one published report. Modified after Schultz-Hector et al., 1995

Figure 2: The dependence of the relative risk of cardiovascular disease incidence (Yamada et al., 2004, A-bomb survivors) or mortality (all other studies) on the mean heart dose corrected for fractionation with the linear quadratic model. (Preston data on A-Bomb survivors, Carr data on radiotherapy for non-malignant disease, Darby and EBCCG data on radiotherapy for breast cancer. modified after Schultz-Hector and Trott, 2007)

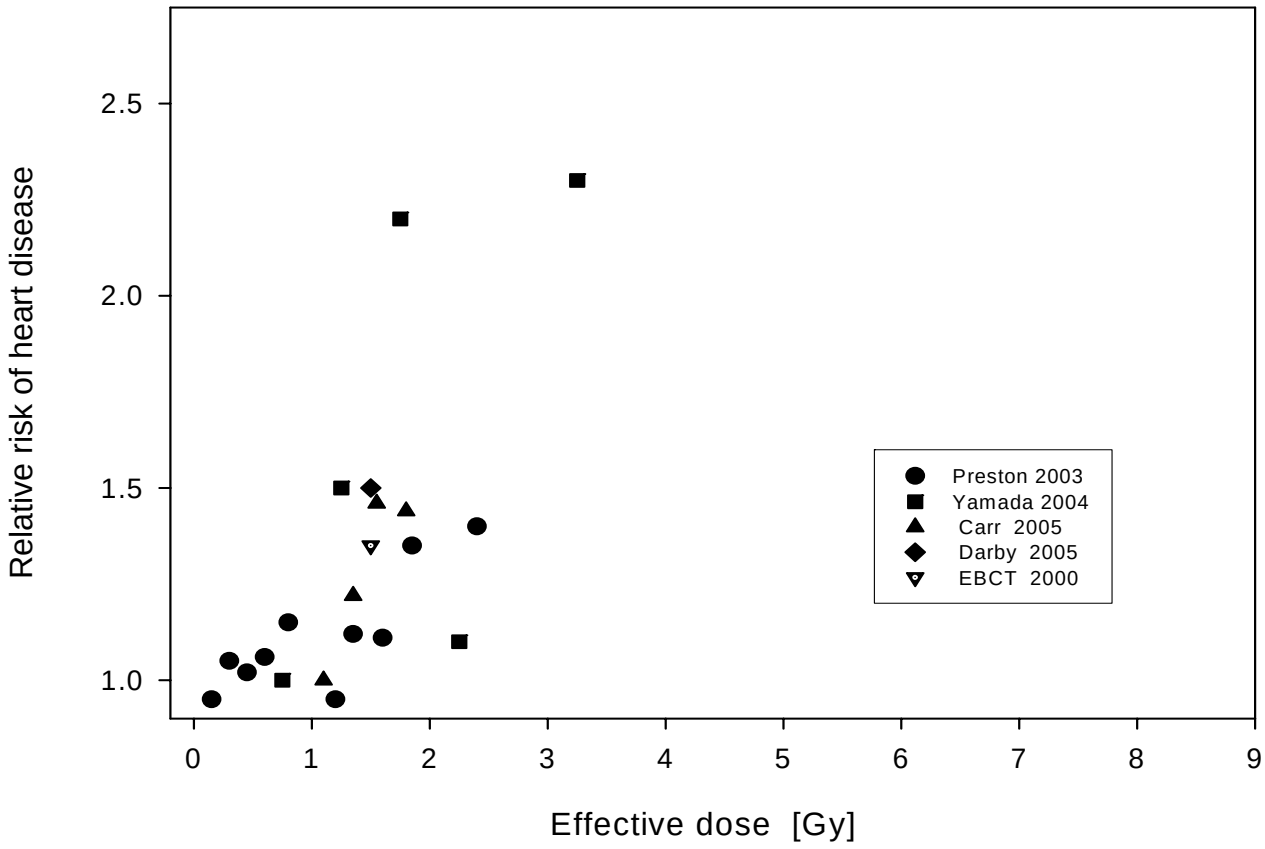

Table 1

Clinical manifestations of radiation-induced heart disease

1. **radiation-induced pericarditis may occur if a large proportion of the heart (>30 %) receives a dose of >50 Gy. The mean latency is approximately 1 year**
2. **radiation-induced myocardial damage may be diagnosed at lower mean doses to the heart. The mean latency is >5 years**
3. **the risk of radiation-induced cardiovascular disease begins to increase 10 years after irradiation and is progressive with time. A significant incrase of risk of cardiovascular disease has been observed after mean heart doses lower than 10% of the generally accepted tolerance dose to the heart of 40-50 Gy fractionated exposure.**

Table 2

Long-term cause specific mortality of 1261 young Hodgkin's disease patients after 13-35 years of follow-up

(data from Aleman et al, 2003)

overall number of deaths	**534**
Hodgkin`s disease	**291**
Second cancer	**116**
Cardiovascular disease	**50**
Ischaemic heart disease	**19**
Myocardial infarction	**16**

Table 3

The risk of cardiovascular disease after post-operative radiotherapy of breast cancer

(data from Darby et al., 2005)

study design

308861 women included in the SEER programme who were treated for breast cancer between 1873 and 2001. 115165 (37%) had received radiotherapy as part of primary treatment. The response criterion was death from cardiovascular disease in relation to the laterality of the breast cancer (left versus right).

results

1. **Of those 4130 women who died after >10 years, 1721 (42%) died from breast cancer, but 894 (22%) died from heart disease**
2. **Post-operative radiotherapy of left-sided breast cancer was associated with a 44% higher risk of death from cardiovascular disease compared to right-sided breast cancer**
3. **Mortality from radiation-induced heart disease increased with time after radiotherapy.**

results of the patient group with >20 years follow-up

time after diagnosis	cardiac deaths		mortality ration
years	left	right	left vs. right
< 5	230	180	1.19
5 – 9	189	145	1.21
10-14	157	106	1.42
>15	234	145	1.58

At no time was there a difference of the cardiac mortality ratio left vs. right breast cancer in those patients who did not receive radiotherapy

Table 4

Ratio of breast cancer deaths and non-breast cancer deaths in breast cancer patients treated with or without radiotherapy

(data from EBCCG 2005)

		follow-up	
		10 years	20 years
breast cancer free survival	with radiotherapy	63.4%	53.4%
	without radiotherapy	60.4%	48.6%
non-breast cancer-free survival	with radiotherapy	90.2%	73.8%
	without radiotherapy	89.2	69.5%

Table 5

Cardiovascular mortality after radiotherapy for peptic ulcer
(data from Carr et al., 2005)

cohort study on 1470 patients treated between 1936 and 1965 for peptic ulcer with radiotherapy compared with 1568 patients treated with drugs
radiation doses to the stomach were 8 – 18 Gy in fractions of 1.5 Gy
radiation doses to the heart were 1.6 – 3.9 Gy in fractions of 0.33 Gy

DOSE DEPENDENCE OF CARDIOVASCULAR RISK

heart dose		number of	cardiovascular	RR
absolute	equivalent single dose *)	patients	deaths	
0 Gy	0 Gy	1568	484	1.0
1.6 Gy	1.2 Gy	363	94	1.0
2.3 Gy	1.4 Gy	384	97	1.2
2.8 Gy	1.7 Gy	341	114	1.5
3.9 Gy	2.2 Gy	382	121	1.5

***) corrected for fractionation with the linear quadratic equation using an α/β ratio of 2 Gy**

Table 6

Mean doses to the heart and the left anterior descending arteria coronaria in patients treated with left tangential radiotherapy for breast cancer
data from Taylor et al., 2007

mean dose	number of patients	
	heart	coronary artery
<1 Gy	2	0
1 – 2 Gy	31	1
2 – 3 Gy	14	11
3 – 4 Gy	3	5
4 – 6 Gy	0	8
6 – 8 Gy	0	5
8 – 10 Gy	0	6
10 – 12 Gy	0	5
12 – 14 Gy	0	6
14 – 16 Gy	0	2
21 Gy	0	1

Table 7

Myocardial perfusion and other functional studies in the hearts of 36 young breast cancer patients 6 – 10 years after radiotherapy

data from Seddon et al., 2005

Functional abnormality	left-sided breast cancer	right-sided breast cancer
perfusion defect	17/24	2/12
irreversible defect	10/24	0/12
abnormal wall motion	8/24	0/12
myocardial damage	10/24	0/12
coronary artery injury	10/24	0/12