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Review

Late radiation-induced heart disease after radiotherapy. Clinical importance, radiobiological mechanisms and strategies of prevention

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ABSTRACT

The clinical importance of radiation-induced heart disease, in particular in post-operative radiotherapy of breast cancer patients, has been recognised only recently. There is general agreement, that a co-ordinated research effort would be needed to explore all the potential strategies of how to reduce the late risk of radiation-induced heart disease in radiotherapy. This approach would be based, on one hand, on a comprehensive understanding of the radiobiological mechanisms of radiation-induced heart disease after radiotherapy which would require large-scale long-term animal experiments with high precision local heart irradiation. On the other hand – in close co-operation with mechanistic in vivo research studies – clinical studies in patients need to determine the influence of dose distribution in the heart on the risk of radiation-induced heart disease. The aim of these clinical studies would be to identify the critical structures within the organ which need to be spared and their radiation sensitivity as well as a potential volume and dose effect. The results of the mechanistic studies might also provide concepts of how to modify the gradual progression of radiation damage in the heart by drugs or biological molecules. The results of the studies in patients would need to also incorporate detailed dosimetric and imaging studies in order to develop early indicators of impending radiation-induced heart disease which would be a pre-condition to develop sound criteria for treatment plan optimisation.

The clinical importance of late radiation-induced heart disease in radiotherapy

The clinical importance of radiation-induced heart disease has been recognised for many years. Traditionally, the tolerance dose of the heart has been estimated at about 40 Gy (whole organ) and even higher for partial volume exposure. These estimates are reasonable for endpoints like pericarditis. The first indication of the relative radiosensitivity of the heart came from long-term follow-up studies of patients treated with mantle field radiotherapy of Hodgkin's disease. These studies in Hodgkin's disease patients demonstrated that radiation-induced heart disease may assume three different clinical manifestations which are 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).

The topic of radiation-induced heart disease has attracted much interest in the past 10 years and there have been a number of good reviews, however, they either concentrate on describing the clinical evidence [1,2] or on the potential importance for radiation protection regulations [3,4]. This paper, however, will focus on the possible radiobiological mechanisms involved in the development of radiation-induced cardiovascular disease after low, intermediate and high radiation doses and how their better understanding might help to develop strategies to reduce this risk in cancer patients treated with radiotherapy.

In recent years, the high rate of ischaemic heart disease in Hodgkin's patients which usually occurs more than 10 years after radiotherapy has attracted particular attention. The Amsterdam cohort study of more than 1200 Hodgkin's disease patients by Aleman et al. is a good example of such a study [5,6]. After a follow-up of 13 to 35 years, 534 out of 1261 young Hodgkin's disease patients had died, 291 (23%) from Hodgkin's disease, 116 (9%) from a second cancer, 50 (4%) from cardiovascular disease, both ischaemic heart disease and myocardial infarction.

The most important message is that despite the relatively 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 the recurrence of the treated cancer.

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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 increase 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

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 40 Gy and higher in large parts of the heart. Vordermark et al. were among the first to use modern treatment-planning methods to reconstruct, in retrospect, dose distributions in Hodgkin's patients many years after the treatment in order to relate findings of functional imaging of the hearts of irradiated patients to those dose distributions [7,8]. In this study, treatment techniques were rather unusual and consisted only of a single ap field encompassing the target volume resulting in inhomogenous dose distribution with significant overexposure of the anterior mediastinum. Nevertheless, the results of the functional-imaging investigations cause concern, in particular the unexpected high frequency of vascular, mostly microvascular perfusion changes and haemodynamically relevant valvular dysfunction [7]. Modern treatment 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. These concepts significantly reduced the need to irradiate the entire mediastinum encompassing the heart. 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 of cardiovascular mortality among the Life Span Study cohort of the Japanese A-bomb survivors stimulated a number of studies in radiotherapy patients [9,10].

In breast cancer patients, part of the heart is exposed to the target dose of between 40 and 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 [11]. 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 significant increase in mortality from ischaemic heart disease [12]. This finding initiated a larger number of 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 the 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 microcirculation [13].

Despite these reports in the early nineties, it is only recently that radiotherapy-associated cardiovascular disease has been recognised by radiation oncologists as a relevant clinical problem. The first time that radiotherapy-induced heart disease was given a special symposium at an international meeting of radiation oncology was in 2005 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 2008 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. Still, no consensus statement or specific recommendations on the issue of radiation-induced cardiovascular disease have been developed so far.

This sudden interest of the radiotherapy community in very late-occurring radiation damage to the heart was further 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.

The Surveillance, Epidemiology and End Results (SEER) cancer registry data base provides 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 [14]. Also using the SEER data, Darby et al. demonstrated the most significant evidence that the risk continuously increased with time after radiotherapy (Table 2, [15]). 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-sided and after 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 diseases. This excess of fatal heart disease represents 4.3% of all deaths of female patients surviving more than 10 years and 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 <0.25 Gy, after correction for fractionation is equivalent to an additional single dose of about 1.5 Gy which could be regarded as the cause of the increased risk of cardiovascular death by 44%. The excess risk is not significant in the first 10 years after the 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

Table 2
The risk of cardiovascular disease after post-operative radiotherapy of breast cancer (data from Darby et al., 2005, [11]).

Results of the patient group with >20 years follow-up			
Time after diagnosis years	Cardiac deaths		Mortality ratio left vs. right
	Left breast	Right breast	
<5	230	180	1.19
5–9	189	145	1.21
10–14	157	106	1.42
>15	234	145	1.58

between 1973 and 1982 and between 1983 and 1992 were also analysed separately. There is a decreasing trend for risk in later cohorts with follow-up of <10 years, yet confidence limits for the later period of 10–15 years are large and the expected improvements from the advances in radiotherapy techniques with regards to very late radiation-induced heart disease have not been proven so far. In a systematic review, Demirci et al. reported on radiation-induced cardiac toxicity after post-operative radiotherapy for breast cancer [16]. Although a steady decrease in cardiac morbidity was observed with the more recent treatments techniques, the modern studies lacked longer follow-up, i.e., more than 10 years. They concluded that the long-term safety of 'modern' radiotherapy of breast cancer is still uncertain.

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 in 2005 [17]. 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 10–20 years after the 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 but (Table 3) also to reduce the risk of death from breast cancer, including death from distant metastasis that was significantly reduced. However, this clinical benefit relating to death from cancer did not translate into a 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 and the micro-vasculature of the heart.

Also single institution studies such as those performed in the Netherlands Cancer Institute by Hooning et al. provided important additional information, in particular with regard to treatment details [18,19]. Whereas post-operative radiotherapy after mastectomy increased the risk of cardiovascular death twofold, 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 did not find a significant influence of irradiated heart volume on cardiovascular radiation risk [20]. 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 clinical importance of the problem, they cannot help solving the problem. The key problem which anatomical structures are important for the risk and which define the dose response relationship can best be investigated in smaller but more detailed studies. The most important of those studies is the Euratom FP6 project: Radiation Associated Cardiovascular Events, the RACE study (details in last section).

Also radiotherapy of non-malignant disease has been shown to be a significant cause of radiation-induced heart disease (Table 4; [21]). 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 the gastric secretion of hydrochloric acid. A similar number of patients suffering from the same disease but treated with drugs were selected as the 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.

Table 3
Ratio of breast cancer deaths and non-breast cancer deaths in breast cancer patients treated with or without radiotherapy (data from EBCCG 2005, [13]).

	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	89.2	69.5
Without radiotherapy	90.2	73.8

Table 4
Cardiovascular mortality after radiotherapy for peptic ulcer (data from Carr et al., 2005 [17]).

Mean heart dose		Number of patients	Cardiovascular deaths	RR
Absolute (Gy)	Equivalent single dose[a] (Gy)			
0	0	1568	484	1.0
1.6	1.2	363	94	1.0
2.3	1.4	384	97	1.2
2.8	1.7	341	114	1.5
3.9	2.2	382	121	1.5

[a] Corrected for fractionation with the linear quadratic equation using an α/β ratio of 2 Gy.

In all radiotherapy studies and scenarios, there is pronounced heterogeneity of doses within the heart. It has been demonstrated already by the Stockholm group 10 years ago that dose and volume appear to be important parameters defining cardiovascular radiation risk [18]. As a first approximation, Schultz-Hector and Trott 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 [[21], Schultz-Hector, 2007 #7]. Despite the great differences in dose distribution between all the 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 a 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.

The clinical importance of radiation-induced heart disease, in particular in post-operative radiotherapy of breast cancer patients, has been recognised by several major radiation oncology societies. The results of the epidemiological studies described above emphasise the need to explore all potential strategies of how to reduce the late risk of radiation-induced heart disease in radiotherapy. There is general agreement, that a co-ordinated research effort would be needed to achieve this goal. This approach would be based, on the one hand, on a comprehensive understanding of the radiobiological mechanisms of radiation-induced heart disease after radiotherapy which would require large-scale long-term animal experiments with high precision local heart irradiation. On the other hand – in close co-operation with mechanistic in vivo research studies – clinical studies in patients need to determine the influence of dose distribution in the heart on the risk of radiation-induced heart disease. The aim of these clinical studies would be to identify the critical structures within the organ which need to be spared and their radiation sensitivity as well as a potential volume and dose effect. The results of the mechanistic studies might also provide concepts of how to modify the gradual progression of radiation damage in the heart by drugs or by biological molecules. The results of the studies in patients would need to also incorporate detailed dosimetric and imaging studies in order to develop early indicators of impending radiation-induced heart disease which would be a pre-condition to develop sound criteria for treatment plan optimisation.

The radiobiological mechanisms of radiation-induced heart disease after radiotherapy

After the ground-breaking pathological and experimental studies of Luis Fajardo in the 1970s, most experimental work on the radiobiology of radiation-induced heart disease was performed by Susanne Schultz-Hector (resp. Susanne Lauk, both are the same person). It was based on high precision X-ray irradiation of the heart in rats after individual beam shaping in every animal and for each dose of the fractionated irradiation to reduce lung exposure as much as possible, since there is marked mutual functional interaction between radiation-induced heart disease and radiation pneumopathy [22].

Congestive heart failure developed many months after the irradiation. With decreasing radiation dose, latency to heart failure increased. There is a clear dose dependence not of damage incidence but of damage progression rate [23]. Latency to heart failure, thus, is the most relevant criterion for studying the modifying effects such as dose fractionation. Plotting median latency versus dose in a large fractionation experiment with up to 10 fractions yielded a very low alpha/beta ratio of <3 Gy [24,25].

Pathology at the time of heart failure of rats after local irradiation shows foci of myocardial necrosis which are not related to the distribution of major blood vessels. In wild-type rats, there is no fibrosis in contrast to humans and rabbits. These findings were interpreted as evidence that myocardial fibrosis is not the primary radiation effect but a reparative response of the heart tissue to radiation damage to other target structures, namely the micro-vascular system. Whereas the primary radiation effect on the microvasculature may be similar in all the animal species, the secondary response of the myocardium appears to depend on the genetic disposition leading either to focal tissue necrosis or to fibrosis.

The focal myocardial degeneration in the irradiated rat heart occurred in the centre of foci of capillary loss. The focal ischaemia can be visualised by angiography. Serial histo-pathological investigations revealed that these foci of ischaemia and necrosis start very small and steadily increase in size until heart failure terminated the experiment.

Progressive decrease of capillary density occurred both as a random rarefication by disappearance of individual capillaries and as a focal loss of groups of capillaries which gradually lead to ischaemic necrosis. Before the focal loss of capillaries, focal loss of alkaline phosphatase activity was observed [26,27]. This focal functional injury of endothelial cells is detectable within few weeks after irradiation, already. Focal loss of capillaries is preceded by increased endothelial proliferation but in the enzyme-negative areas only [28].

Cardiac output did not decrease progressively. There was a modest, early decrease of cardiac output, however, after this drop, cardiac output remained stable until the final heart failure [29]. The concentration of beta-adrenoceptors in the irradiated heart increased by 50%, already 2 months after the irradiation, before any evidence of myocardial damage was apparent [29]. This suggests that the initial radiation damage stimulated an up-regulation of cardiac output to a stable level via adrenergic mechanisms until the breakdown of compensatory ability. At the time of beginning congestive heart failure, a sudden drop of left ventricular ejection fraction and of cardiac output has been measured [30]. This means that cardiac output is not a safe criterion of sub-clinical radiation damage to the heart, neither in experimental animals nor in patients.

Schultz-Hector and Trott concluded that in rodents, radiation-induced heart disease was caused by radiation damage to the micro-vasculature leading to focal ischaemia [11]. Atherosclerosis to the coronary arteries was never observed in rodent hearts except in constitutionally hypertensive rats [31]. Yet it has to be considered that wild-type rodents are not a good model for atherosclerosis since they have extremely low levels of low density lipoproteins (unlike humans) and do not develop age-related atherosclerosis unless kept on very high fat diets.

Research into the pathogenesis of radiation-induced atherosclerosis in large arteries is relatively recent and predominantly performed by the radiobiologists of the Netherlands Kanker Institute in Amsterdam in co-operation with the cardiovascular research unit in Maastricht, Holland, using genetically modified APO-E knock-out mice [32,33]. These rodents develop atheromas spontaneously within 6–12 months and are the favourite animal model for investigating factors which affect the development of atherosclerosis in humans. A radiation dose of 8 Gy speeds up the development of spontaneous atherosclerotic plaques and changes their phenotype into a more unstable, inflammatory type which is prone to rupture causing thrombosis.

From the present state of understanding of the pathogenesis of radiation-induced cardiovascular diseases in experimental animals it may be concluded that radiation may cause both types of cardiovascular disease: micro-vascular disease which is characterised by a decrease in capillary density causing chronic ischaemic heart disease and focal myocardial degeneration, and macro-vascular disease through the faster development of age-related atherosclerosis in the coronary arteries [11].

The cellular and molecular mechanisms of cardiovascular radiations risks at low, intermediate and high radiation doses

The epidemiological studies, so far, do not give unequivocal information about which types of cardiovascular diseases are induced by radiation. However, in order to design preventive or therapeutic, interventional strategies it is important to find out which type is occurring after different irradiation conditions. It is likely that the development of either macro- or micro-vascular damage after radiation exposure will be dependant on dose, dose distribution and other risk factors present in various animal strains and humans. Moreover, both types of radiation-induced heart disease may show different latencies at different dose levels.

The current European cardiovascular radiation risk research project CARDIORISK (www.cardiorisk.eu) aims at the investigation of the cellular and molecular mechanisms of cardiovascular radiation risks at low, intermediate and high radiation doses. This project is largely based on the results of the experimental studies on the possible mechanisms of radiation-induced heart disease described above. It includes 11 partners from all over Europe, all of whom work on identical biological material which is centrally produced and distributed to the partners who use their particular expertise and methods to address a wide range of mechanistic questions. High precision local irradiation of the hearts with low (0.2 Gy), intermediate (2 Gy) and high (12–20 Gy) radiation doses is performed in Amsterdam and Dresden in C57Black mice and in APO-E mice. Animals are followed up for up to 18 months after the irradiation.

The experimental design is targeted to test two alternative hypothesis of the biological mechanisms leading to cardiovascular death after different radiation doses.

Hypothesis 1. Radiation increases the frequency of myocardial infarction by interacting with one or more steps of the pathogenic pathway of age-related coronary artery atherosclerosis. This hypothesis is supported by recent findings on coronary artery changes in patients after post-operative radiotherapy for breast cancer [34,35].

Hypothesis 2. Radiation increases the lethality of myocardial infarction, which may occur due to pathologies unrelated to radiation, i.e. by reducing the organ tolerance to minor acute infarctions as a result of persistent or progressive reduction of the microcirculation in the irradiated heart [36].

Therefore, in addition to investigating hearts after local heart irradiation, CARDIORISK also looks at functional and pathological changes in the arteria carotis and the arteria saphena after local irradiation. Functional imaging of the micro-vasculature of the heart and the vascular patency of the irradiated arteries is being performed at regular intervals using micro-positron emission tomography (PET), optical coherence tomography (OCT). Histopathological investigations are being performed by 6 different partners using different methods and criteria: The main criterion in the hearts is micro-vascular density and evidence for focal hypoxia in relation to the changes observed by functional imaging. Additionally, changes in inflammatory and pro-thrombotic factors are being studied by immunohistochemistry. The main criterion in the arteries is the size and inflammatory features of potential atheromatous plaques. Ex vivo investigations of the irradiated arteries investigate intercellular signalling and, in particular, the endothelium-leukocyte interactions and pro-thrombotic alterations of the endothelium. Endothelial cells are being isolated from irradiated hearts at different times after local irradiation as these are considered to play a key role in cardiovascular radiation risks. Stress responses, changes in intercellular communication, changes in three-dimensional remodelling and migration, in particular in co-culture with cardiomyocytes, changes in endothelial permeability and cyto-skeleton structure and pro-inflammatory and pro-thrombotic changes are also studied. Proteomics investigations identify changes in the protein constitution of irradiated hearts and endothelial cells at different times after the irradiation.

So far, the CARDIORISK project has been developing methods and techniques of local heart irradiation in mice with good lung sparing, of isolation of myocardial and endothelial cells from the heart of mice irradiated up to 60 weeks before, of morphometric analysis of capillary density and endothelial function ex vivo and analysis of changes in the endothelial function of isolated endothelial cell sheets prepared from irradiated endothelial cells months after the irradiation. After completion, the project will have produced a plethora of information on potential radiation effects on a wide range of functions of the cardiovascular system, in particular in micro-vascular and macro-vascular endothelial cells. The entire project concentrates on early and late functional changes in putative target cells and tissues, which until recently have been seriously neglected in radiation biology research. It is anticipated that the results of the CARDIORISK project will lead to new concepts for designing further studies on the radiobiological mechanisms of radiation-induced heart diseases after low, intermediate and high radiation doses and potential strategies to reduce those risks.

Strategies of prevention of radiation-induced heart disease in radiotherapy

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 of late radiation-induced heart disease, 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 dose to the heart 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 the 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 localization 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 by the RACE project demonstrate that this is difficult but possible [37,38].

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 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. 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 the 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, since calculated mean heart doses changed very much over time. They were highest in the seventies and have steadily fallen since and continue to do so. This is due to changes in target definition, changes in treatment technique, and probably mostly due to the 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 cardiovascular radiation risk.

Future clinical studies in radiotherapy patients should link the results of the mouse studies with the results of the epidemiological studies to develop early indicators of late radiation-induced heart disease. The most promising approach involves clinical studies based on modern non-invasive imaging procedures such as single photon emission computed tomography (SPECT), PET, ultrasound imaging (US) and combined computed tomography (CT) and 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 5, [13,39–41]). Repeated investigations of myocardial perfusion of a large group of patients over 3–8 years after radiotherapy with abnormalities at earlier time-points demonstrated that perfusion defects persist in the majority of patients. Darby et al. concluded that "as the perfusion abnormalities follow the contour of the radiation treatment field, rather than the territorial distribution of coronary

Table 5
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., 2002 [37]).

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

arteries it appears that they represent a radiation-related micro-vascular injury to the myocardial capillary network" [36]. For many years these perfusion changes were not associated with clinical signs and symptoms of ischaemic heart disease. However, after more than 5 years, wall motion abnormalities and other pathological changes of heart function were observed in patients with persisting perfusion defects using functional imaging. In contrast to the micro-vascular changes in breast cancer patients, long-term follow-up in patients with Hodgkin's disease did not reveal an association of regional pathological changes and reconstructed dose [7]. Darby et al. concluded that "as patients are known to be at increased risk of cardiac events after more than 10 years post breast radiotherapy, it is tempting to hypothesize that these perfusion defects are related in some way to the longer-term clinical manifestations" of radiation-induced heart disease after radiotherapy [36].

Several studies are in preparation with the aim of relating those changes in functional imaging and their gradual progression to the individual dose distribution within the organ heart. The main emphasis would be on well controlled new prospective cohort studies in breast cancer patients with very different dose distributions in the heart due to anatomical features and/or treatment techniques (including brachytherapy) as well as studies in retrospectively established cohorts of breast cancer patients with good information on individual dose distribution in the hearts. These patients would need to be investigated at regular intervals with various imaging methods for defects of micro-vascular perfusion and heart function as well as for signs and symptoms of ischaemic heart disease. Particularly in young breast cancer patients such clinical studies would seem to be justified also from the clinical standpoint for the benefit of the individual patient who could be treated with drugs identified in experimental systems as having preventive potential or should be advised to change life-style factors which are likely to increase the risk or the severity of radiation-induced heart disease.

Experimental studies in rats showed a possible protective effect of postirradiation treatment e.g., with pentoxyphyllin on the development of functional radiation cardiomyopathy [42]. This approach shouldbeexpandedandnewpromisingconceptsofdelayingtheclinical manifestations of progressive ischaemic heart disease should also be tested in radiation-induced heart disease (particularly in rats). Close co-operation with cardiovascular research groups unrelated to radiotherapymaybeessentialtoguaranteesuccess.However,untilsafepostirradiation treatment for secondary prevention of radiation-induced heart disease becomes available, the strategies of prevention have to concentrateontheidentificationofcriteriaforoptimisingdosedistributionintheheart,inparticularinyoungerpatientswithleft-sidedbreast cancer.

Conclusion

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 the effective dose to be corrected with an organ-weighting factor in radiation protection?

The real challenge will, however, come only after all the data have been collected e.g. in the CARDIORISK project, namely, judging the contribution of each of those effects towards the development of clinical disease of the cardiovascular system. Inevitably, there is a huge gap between the experiments in mice and the medical problems. This gap can only be bridged by future co-ordinated research programmes which aim specifically at investigating, in exposed humans, cardiovascular alterations which have been found to be associated with the radiation effects in rodents but which may also be involved in the clinical response of the irradiated organs more than 10 or 20 years later.

The main problem of clinical research into radiation-induced cardiovascular risk is the extremely long latency to symptomatic disease. The early perfusion changes which can be precisely quantified and recorded anatomically with modern non-invasive imaging techniques may prove ideal for the way forward. These changes occur early enough to develop, for example criteria of treatment plan optimisation in the radiotherapy of breast cancer patients. A comprehensive clinical and translational research programme should address a range of open questions, all of which may have an impact on the choice and delivery of post-operative radiotherapy techniques:

1. Which patients are at risk for radiation-induced cardiovascular disease (CVD)? What are the effects of additional treatments (surgery, chemotherapy)?
2. Which types of heart disease are induced by modern radiotherapy, especially for breast cancer? Is there a dependency of type of radiation-induced heart disease depending on dose and latency?
3. What are the main criteria for treatment plan optimisation: dosimetric parameters, volume or anatomical structures? How should cardiotoxic chemotherapy influence plan optimisation?
4. How long should patients be followed and which type of clinical, cardiological and imaging examinations should be performed?
5. Which medication should be given to patients at risk and when?
6. How should competing risks, in particular local tumor recurrence, radiation-induced cancer and radiation-induced CVD be incorporated and balanced in treatment plan optimisation?

Conflict of interest

M. Molls is coordinator, N. Andratschke scientific manager, J. Maurer scientific assistant and K.R. Trott member of the advisory board of the FP7 collaborative research project CARDIORISK.

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