Cardiovascular disease after cancer therapy

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ABSTRACT

Improvements in treatment and earlier diagnosis have both contributed to increased survival for many cancer patients. Unfortunately, many treatments carry a risk of late effects including cardiovascular diseases (CVDs), possibly leading to significant morbidity and mortality. In this paper we describe current knowledge of the cardiotoxicity arising from cancer treatments, outline gaps in knowledge, and indicate directions for future research and guideline development, as discussed during the 2014 Cancer Survivorship Summit organised by the European Organisation for Research and Treatment of Cancer (EORTC).
Better knowledge is needed of the late effects of modern systemic treatments and of radiotherapy to critical structures of the heart, including the effect of both radiation dose and volume of the heart exposed. Research elucidating the extent to which treatments interact in causing CVD, and the mechanisms involved, as well as the extent to which treatments may increase CVD indirectly by increasing cardiovascular risk factors is also important. Systematic collection of data relating treatment details to late effects is needed, and great care is needed to obtain valid and generalisable results.
Better knowledge of these cardiac effects will contribute to both primary and secondary prevention of late complications where exposure to cardiotoxic treatment is unavoidable. Also surrogate markers would help to identify patients at increased risk of cardiotoxicity. Evidence-based screening guidelines for CVD following cancer are also needed. Finally, risk prediction models should be developed to guide primary treatment choice and appropriate follow up after cancer treatment.

1. Introduction

Improvement in treatment modalities, including radiotherapy and systemic therapies, has led to better prognosis for patients with malignancies [1–3]. Unfortunately, they may also induce late effects including an increased risk of cardiovascular disease (CVD) in long-term survivors [3,4]. In the general population CVDs are major causes of morbidity [5] and

mortality, accounting for 30–50% of all deaths in most developed countries. Because of this high background rate, even a minor increase in risk of CVD will have an important impact on morbidity and mortality.

Heart disease following cancer treatment may be the result of direct cardiovascular damage caused by the treatment itself or of accelerated atherosclerosis due to cancer treatment-related cardiovascular risk factors [5]. We will address both aspects. In this paper we will summarise the discussion regarding current knowledge and future research goals from a dedicated workshop which took place at the 1st Cancer Survivorship Summit organised by the European Organisation for Research and Treatment of Cancer (EORTC) (January 30, 2014, Brussels, Belgium) and focus on treatment related heart disease in adult cancer survivors.

2. Current knowledge and gaps in knowledge

2.1. Radiotherapy-related cardiotoxicity

2.1.1. Current knowledge
Radiation-related heart disease includes a variety of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, pericarditis and valvular heart disease [6–8]. Electrical conduction abnormalities have also been reported but data are less consistent. Radiation-related pericarditis usually occurs shortly after exposure. Other radiation-related heart diseases typically present 10–15 years later [4,7]. Radiation-related ischaemic heart disease (IHD) is generally observed at a younger age than IHD in the general population [9–11].

The magnitude of the problem depends on both patient and treatment characteristics (See Tables 1–3). Evidence for a dose-dependent relationship for radiation-related heart disease is accumulating [8,12–14]. Exposure of the heart to even a low radiation dose may lead to an increased risk. A significantly increased risk of death from heart disease (with a linear dose–response relationship) has been observed among the Japanese atomic bomb survivors during the 40 years after exposure to a single dose of <4 Gy [15,16]. Patients treated

for peptic ulcer with radiotherapy to the stomach had an increased risk of coronary heart disease which increased with heart dose (p trend = 0.01)[12]. Increased risks of morbidity and mortality from CVD have also been observed after treatment for Hodgkin lymphoma [9,17,18]. Reducing the radiation dose to the heart by shielding a part of the heart (using a sub-carinal block) reduced the relative risk for cardiac diseases other than myocardial infarction (MI) [17].

Increased mortality and morbidity from heart disease has also been reported after radiotherapy for breast cancer (BC), especially after some of the radiotherapy techniques that were used in the past [19,20]. Studies on cardiovascular toxicity following radiation for BC frequently compare patients with left-sided and right-sided BC or compare BC patients with the general population (taking into account sex, age and calendar period; see Table 3). Studies comparing patients who have been irradiated with those who have not have also been carried out but, unless they are part of a trial in which patients have been allocated to radiotherapy at random, care must be taken when interpreting them, as patients selected for radiotherapy may differ from other patients in terms of their baseline risks.

In a recent publication 963 women who experienced a major coronary event after radiotherapy for BC between 1958 and 2001 in Sweden and Denmark were compared with 1205 control women who were also irradiated for BC but did not have a major coronary event [14]. An increased risk of major coronary events was observed that started within the first 5 years after radiotherapy and continued into the third decade. The major coronary event rate increased linearly with the mean dose to the heart by 7.4% per Gy (95% confidence interval, 2.9–14.5; P < 0.001), with no apparent threshold.

Classical risk factors for coronary artery disease also influence the risk of radiation-related CVDs. Higher risks of developing CVDs following exposure of the heart to radiation have been observed in patients with classical risk factors for CVDs [21]. For example in a large study in 10-year survivors of BC, smoking and radiotherapy together were associated with an even more than additive effect on risk of MI [22].

Table 1 – Excess risks of cardiac mortality after Hodgkin lymphoma therapy over time.									
Median age in years (range)	Stanford Hoppe et al. [82] (1997) Not reported		Harvard Ng et al. [83] (2002) 25 (3–50)		The Netherlands Aleman et al. [84] (2003) 25.7 (2–40)		BNLI[*] Swerdlow et al. [11] (2007) Approximately 30 years (all ages)		CCSS Castellino et al. [10] (2011) 14 (2–20)
Interval (years)	RR	AER	RR	AER	RR	AER	RR	AER	AER
0–5	2	6.4	4.4	6.3	7.6	6.1	1.7	4.6	–
5–10	3.6	20.1	2.7	5.3	7.0	10.6	2.3	10.9	5.1
10–15	3.0	20.5	2.5	7.2	4.5	10.7	1.9	8.5	12.3
15–20	5.0	54.2	2.8	13.9	6.8	28.7	4.1	28.9	12.3
>20	5.6	70.6	4.5	41.1	8.3	53.9	3.1	22.2	25

Adapted from "Long-term complications of lymphoma and its treatment" Ng et al. [85].
Between brackets: year of publication.
BNLI, British National Lymphoma Investigation; CCSS, Childhood Cancer Survival Study; RR, relative risk; AER, absolute excess risk per 10,000 person years.
[*] Death from myocardial infarction only.

Table 2 – Excess risks of cardiac morbidity after Hodgkin lymphoma therapy.

	University of Florida Hull et al. [86] (2003)	The Netherlands Aleman et al. [9] (2007)		Princess Margaret Hospital Myrehaug et al. [26] (2008)		Harvard Galper et al. [87] (2011)	
	RR	RR	AER	RR	AER	RR	AER
CABG	1.63	–	–	–	–	3.2	18
PTCA	–	–	–	–	–	1.6	18
Valve surgery	8.42	–	–	–	–	9.2	14
Pacemaker	–	–	–	–	–	1.9	9
MI/angina pectoris	–	3.2	61.7	–	–	–	–
CHF	–	4.9	25.6	–	–	–	–
Cardiac hospitalisation	–	–	–	1.9	35.6	–	–

CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; CHF, Congestive heart failure; RR, relative risk; AER, absolute excess risk.
Adapted from "Long-term complications of lymphoma and its treatment" Ng et al. [85].

2.1.2. Gaps in knowledge

Although our knowledge concerning radiation-related cardiotoxicity has improved over the last decades there are still many open questions.

Effects of specific doses to the whole heart and to specific cardiac substructures have only been assessed in a few studies [13,14,23]. With the use of more modern radiotherapy-techniques, such as intensity modulated radiotherapy, knowledge about the effects of radiotherapy dose and volume on critical structures of the heart is increasingly important [24].

Furthermore, data on the separate and combined effects of modern radiotherapy and cardiotoxic chemo(immuno)therapy on cardiac disease risk have only been addressed in a small number of studies generally with limited follow-up [9,11,25,26].

Potential interactions between treatment and lifestyle factors (e.g. smoking, hypertension, hypercholesterolemia, premature menopause) need further study especially since improved knowledge may lead to intervention possibilities. Early detection of (sub)clinical cardiac damage may be important but currently there are no specific guidelines for screening on radiation-related cardiac diseases. At present, in order to prevent such diseases, screening can be aimed only at early detection and at treatment of general risk factors for CVD.

Furthermore, there are indications of large inter-individual variation of susceptibility to treatment-related toxicity and of some variation of genetic susceptibility for radiation-related CVD [27], but further studies are needed.

Since clinical end-points often do not occur until at least 10–15 years after exposure and intervention before they occur may be useful, adequate imaging screening tools and surrogate markers are needed for treatment-related cardiac diseases.

Better knowledge concerning risk factors and mechanisms underlying radiation-related CVDs will contribute to primary and secondary prevention of long-term treatment complications in cancer survivors where exposure of the heart to radiation is unavoidable.

2.2. Cardiotoxicity related to systemic therapy

2.2.1. Current knowledge

The variety of cardiovascular side-effects from systemic cancer therapies is diverse and includes the induction of cardiac dysfunction, myocardial ischaemia, arrhythmias, thromboembolism, arterial and pulmonary hypertension, peripheral arterial occlusive disease and pleural effusion (Table 4)[28]. Cardiotoxicity following systemic treatment is typically associated with loss of myocardial mass, leading to progressive cardiac remodelling and dysfunction. Patients experiencing cardiotoxicity develop heart failure (HF) months to years after the initial cancer therapy and have a severely impaired cardiovascular prognosis [29]. Anthracyclines are a well known example of cardiotoxicity; the pathophysiological mechanism is complex but involves dose-related myocardial cell death during cancer treatment and possibly an impairment of reparatory and homoeostatic mechanisms after the exposure to chemotherapy [30,31]. Signalling inhibitors -such as anti-HER2 compounds and angiogenesis inhibitors- were also found to induce cardiac dysfunction. However, in contrast to anthracyclines these drugs typically lead to cardiac dysfunction during cancer treatment with a high potential of reversibility [32]. Furthermore, recent data suggest that patients exposed to trastuzumab have a low risk of progressive cardiac disease even when followed for years after the initial cancer treatment [33]. While cancer drug associated, irreversible cardiotoxicity has recently been termed Type I cardiotoxicity, the reversible form of cardiac dysfunction was named Type II dysfunction [28]. Other cancer drug related cardiovascular side-effects with long-term implications for patients include BCR/ABL tyrosine kinase inhibitor-induced pulmonary hypertension and peripheral arterial occlusive disease [32,34]. These effects typically occur years into treatment with these compounds and the course of the disease remains unclear.

2.2.2. Gaps in knowledge

Although the cardiotoxic risk of conventional chemotherapeutics such as anthracyclines has been recognised for more than 35 years there are still considerable gaps in the

Table 3 – Overview of studies on risk of cardiac disease after RT regimens applied during the 1970s and 1980s.

First author	Study size	Treatment period	RT regimen	Method of comparison	RR: incidence	RR: mortality	Refs
Rutqvist (1990)	54,617	1970–1985	~50 % RT	L versus R-sided tumours	–	MI: 1.09 (1.02–1.17)	[88]
Rutqvist (1998)	5680	1976–1987	Postlumpectomy	RT (12%) versus no RT	MI: 0.6 (0.4–1.2)	MI: 0.4 (0.2–1.1)	[89]
Højris (1999)	3083	1982–1990	Postmastectomy	RT versus no RT	IHD: 0.86 (0.6–1.3)	IHD: 0.84 (0.4–1.8)	[90]
Paszat (1999)	25,570	1982–1987	Postlumpectomy	L versus R-sided RT	–	MI: 2.10 (1.11–3.95)	[91]
Vallis (2002)	2128	1982–1988	Postlumpectomy	L versus R-sided RT	MI: no difference	MI: no difference	[92]
Darby (2003)	89,407	1970–1996	~30% RT	L versus R-sided tumours	–	CVD: 1.10 (1.03–1.18)	[93]
Giordano (2005)	27,283	1973–1989	Several	L versus R-sided RT	–	IHD†: 1.5 (1.19–1.87)	[94]
Darby (2005)	115,165	1973–1901	Several	L versus R-sided RT	–	CVD†: 1.44 (1.26–1.65)	[54]
Patt (2005)	16,270	1986–1993	Several	L versus R-sided RT	IHD: 1.05 (0.94–1.16)	–	[95]
EBCTCG (2005)	32,800	1961–1991	Several	RT versus no RT	–	CVD: 1.27 (2p = 0.0001)	[2]
Harris (2006)	961	1977–1994	Postlumpectomy	L versus R-sided RT	IHD: 2.7 (1.7–4.5)	CVD: no difference	[21]
Hooning	7425	1970–1986	Several	RT versus no RT	–	CVD: 2.07 (1.35–3.29)	[96]
Hooning	4414*	1970–1986	Several	RT versus no RT	1970–1970 MI: 2.77 (1.62–4.75) 1980–1986 MI: 0.87 (0.47–1.59)		[22]

L, left; R, right; RT, radiotherapy; RR, relative risk; MI, myocardial infarction; CVD, cardiovascular disease; IHD, ischaemic heart disease; EBCTCG, Early Breast Cancer Trialists Collaborative Group. Adapted from thesis M.J. Hooning titled Adverse effects of treatment in long-term survivors of breast cancer.

* 10-year survivors[22].

† IHD mortality among women diagnosed after 1979 mortality from ischemic heart disease declined by 6% for each successive year until 1988 (HR, 0.79; 95% CI: 0.52–1.18).

understanding of the mechanisms, individual risk factors and prevention of this side-effect (See Table 5). The cardiotoxicity problem is increasing since the introduction of anti-cancer signalling inhibitors that have the potential of causing cardiac dysfunction itself or increasing cardiotoxicity of conventional chemotherapeutics [35]. At present, there is no universally accepted definition of cardiotoxicity and many of the more recent clinical trials that investigated potentially 'cardiotoxic' cancer drugs did not differentiate between Type I cardiotoxicity and Type II cardiac dysfunction. Furthermore, since the full spectrum of cardiotoxicity frequently does not become apparent until months or even years after the initial cancer treatment, long-term follow-up of patients exposed to potentially cardiotoxic cancer drugs is needed and early surrogate markers predicting long-term cardiovascular prognosis are wanted. These predictive markers need to be universally applicable and detect early myocardial loss by, for example, measuring high-sensitivity cardiac biomarkers [36]. However, some of the early work with cardiac biomarkers for the prediction of cardiotoxicity has been challenging because the dynamics of biomarker release after chemotherapy was unknown and long-term data confirming the predictive value are missing [37]. It has become clear that the decrease in left ventricular ejection fraction measured either by echocardiography or nuclear scans is not very sensitive in predicting which patient eventually develops cardiotoxicity [31]. Newer imaging techniques such as myocardial strain and strain rate Doppler echocardiography may be more accurate and sensitive to detect early changes of cardiotoxicity [38]. However, these methods may have technical limitations particularly in BC patients after left-sided surgery. Numerous preventive strategies to mitigate cardiotoxicity particularly of anthracyclines have been investigated. They included alterations of the chemical structure, liposomal encapsulation or co-medications to reduce iron chelation. Although some of these strategies appeared successful in reducing cardiotoxicity, questions of impaired efficacy and possible induction of second tumours arose [28]. Global guidelines to treat cardiac dysfunction recommend the early use of renin-angiotensin inhibitors and beta blockers. Although these drugs have been tested to attenuate anthracycline-associated cardiotoxicity in single centre studies, convincing evidence from large randomised multicentre trials are still missing [39]. Finally, although several risk factors for anthracycline-associated cardiotoxicity have been identified, individual risk assessment in patients based on genomics and proteomics is still missing. The recent preclinical discovery that topoisomerase-IIbeta may mediate anthracycline-associated cardiotoxicity opens exciting new options: the opportunity to develop topoisomerase-IIalpha specific anthracyclines that are likely less cardiotoxic and also the potential to predict patient's individual risk for anthracycline-associated cardiotoxicity based on their individual topoisomerase-IIbeta expression [40].

2.3. Metabolic syndrome

2.3.1. Current knowledge
The metabolic syndrome is a clustering of metabolic disorders that is associated with a twofold increased risk of CVD compared to the general population. Key components of the

Table 4 – Cardiovascular side-effects of selected systemic cancer therapeutics.

Cardiovascular effect	Cancer therapy	Long-term effect	Mechanism
Cardiotoxicity Type I irreversible	Anthracyclines Cyclophosphamide Cisplatin	Yes Rare Rare	Loss of myocardium Myocarditis Unknown
Cardiac dysfunction Type II reversible	Anti-HER2 Therapeutics Anti-VEGF Therapeutics	Unlikely, except when combined with anthracyclines Unlikely	Mitochondrial dysfunction Mitochondrial dysfunction
Myocardial ischaemia	Pyrimidine analogues Anti-VEGF therapeutics	Rare Rare	Coronary vasospasm Arterial thrombosis
Arrhythmia	Arsenic trioxide Selected TKIs	No	HERG K+ blockage HERG K+ blockage
Thromboembolism	Cisplatin Anti-VEGF Therapeutics	Rare	Endothelial damage Endothelial damage
Arterial hypertension	Anti-VEGF Therapeutics	Unknown	Multiple mechanisms
Pulmonary hypertension	Selected TKIs	Unknown	Unknown
Peripheral arterial occlusive disease	Selected TKIs	Unknown	Unknown
Pleural effusion	Selected TKIs	Unknown	Unknown

Abbreviations: HER2, human epidermal growth factor receptor 2; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor, HERG K+, human ether-a-go-go-related gene K+.

Table 5 – Gaps in knowledge concerning cardiotoxicity related to systemic therapy.

Lack of universally accepted definitions of cardiotoxicity and cardiac dysfunction
Differentiation between irreversible and reversible cardiac dysfunction
Long-term follow-up data (10–20 years) needed
Early surrogate markers to predict long-term cardiovascular prognosis
Early pharmacological intervention to mitigate cardiotoxicity
Individualised patient risk assessment

syndrome are decreased insulin sensitivity, hypertension, overweight and an adverse lipid profile. Unfortunately, different classification systems use different criteria to define the metabolic syndrome, creating heterogeneity in reported prevalence between geographical areas and between study populations [41]. Development of the metabolic syndrome may contribute to increased CVD risk in prostate cancer patients using androgen deprivation therapy (ADT), in survivors of testicular cancer (TC) and of childhood malignancies [42–45].

Following standard cisplatin-based chemotherapy, TC survivors have an increased prevalence of the metabolic syndrome compared with the general male population [46]. The metabolic syndrome develops early (3–5 years) after treatment and is associated with decreased serum total testosterone concentration [47]. Childhood cancer survivors of haematological malignancies, mainly acute lymphoblastic leukaemia, and brain tumours have an increased risk of the metabolic syndrome after cranial, abdominal or total body irradiation [44,48]. Development of the metabolic syndrome in these radiotherapy-treated patients is associated with growth hormone deficiency and hypogonadism. Prostate cancer patients may develop an increase in fat mass, a decrease in lean body mass, an adverse lipid profile, and impaired insulin sensitivity early (within 3–6 months) after start of androgen deprivation therapy ADT [49]. These changes differ from the features of the classically defined metabolic syndrome, since ADT induces accumulation of subcutaneous rather than visceral fat, and an increase rather than a decrease in high-density lipoprotein cholesterol. Finally, components of the metabolic syndrome, including weight gain and adverse changes in lipid levels, have been reported in BC survivors [50]. These changes are associated with hormonal therapy and with development of early menopause due to oophorectomy or chemotherapy.

Because of its relatively high prevalence and because of the effects of the metabolic syndrome in cancer survivors, it should be addressed in future care plans. Interventional studies have shown that individuals who make favourable changes in their lifestyle after cancer diagnosis feel better, experience less fatigue and may possibly even decrease risk of cancer recurrence [51].

2.3.2. Gaps in knowledge
Insight into the aetiology of the metabolic syndrome after cancer treatment might help to identify and treat cancer survivors with an increased CVD risk.

Development of the metabolic syndrome after cancer therapy is associated with endocrine disorders, mainly growth

hormone deficiency and hypogonadism. However, hormonal replacement therapy to counteract adverse metabolic changes can be undesirable from the oncological perspective, as in prostate cancer patients on ADT. Where it is possible, intervention trials to establish the size of any effect of hormonal replacement therapy and its clinical relevance in cancer patients are needed.

Although the metabolic syndrome is associated with an increased CVD risk, other factors, like smoking, genetic predisposition, and co-morbidity also contribute to actual CVD risk. Models incorporating all these factors are needed to better define patients with high and low CVD risk during follow-up.

Current models estimating ten-year CVD risk, like the Framingham risk score, are likely to underestimate the CVD risk, since treatment-related CVD risk certainly continues beyond ten years in cancer survivors. Therefore, life-time instead of ten-year risk predictions for CVD are required for cancer survivor populations. These predictions could identify high risk groups who would benefit from screening and also aid in making treatment decisions.

Finally, the prevalence of the metabolic syndrome in survivors treated with both systemic therapy and radiotherapy is still unknown, but should be assessed during follow-up.

3. Future research

3.1. Learning from the past

There is inevitably uncertainty regarding the long-term effects of the cancer treatments that are currently in use. In contrast, the long-term effects of treatments that have been used in the past can, in principle, be ascertained. However, the treatment that past patients received is now often considered to be outdated. For example, radiotherapy for Hodgkin lymphoma 15–20 years ago consisted of mantle field irradiation up to 40 Gy, a treatment which has little resemblance to the radiotherapy given today [52]. Likewise, systemic treatment has changed substantially during the past few decades. Data on long-term complications from former treatments are still important for long-term survivors treated many years ago. However, they may lead to an exaggerated fear of treatment modalities that have been available for a long time. For example modern radiotherapy approaches generally lead to lower doses to the heart and a dose response relationship has been shown so, lower risks of CVD are expected [53]. There may also be a tendency to underestimate the risks of newer treatment modalities for which long term follow-up information is not available. Nevertheless, the experience of past patients can be one of the richest sources of information on the likely long-term consequences of treatments that are currently in use.

3.2. Randomised trials

One source of information on the long-term experience of patients, is the information collected during the course of phase III trials in which patients satisfying certain prespecified criteria are randomly allocated between two or more different treatment schedules and their subsequent experience compared. Data from large randomised trials performed in the past are particularly useful since treatments were usually standardised, and direct comparisons between treatments are possible.

In general, randomised clinical cancer trials are set up with a time-frame of 5 or 10 years in mind at most. Information on CVD occurring during the first 5 or 10 years is informative [14], but can be of limited use, because many effects may continue into the second decade after treatment [54] and possibly even beyond [4,55]. Therefore, additional follow-up is valuable where it can be obtained. The challenge is to obtain systematic long-term data on patients, since systematic long-term follow-up of patients is expensive and not widely practiced today. Long-term survivorship clinics using dedicated nursing staff and telephone or internet contact with patients may provide a solution.

However, it is often unnecessary to bring patients into the clinic to follow them for late effects, and in several countries useful information can be ascertained at modest cost by matching the list of patients in the trial against national registers of vital status, cause of death and hospital diagnoses [56]. In countries where this is not possible, or where information is required on end-points that are not covered by pre-existing registers, information on late effects can sometimes be obtained by correspondence with the patients themselves [13].

As well as the advantages listed above, randomised studies tend to have some limitations for studying late effects. Individual trials often have very low power for the assessment of late effects (small numbers of patients and/or incomplete data). This difficulty can be overcome by combining information from more than one trial and, preferably, from all the trials carried out in a predefined category, e.g. trials of a particular drug given for a particular cancer. But even this may provide only limited power, especially for cancers in which survival was only moderate at the time the trial was carried out. Many chemotherapy drugs are, however, used for several different cancers and for these drugs, information on late effects from trials carried out in different cancers can be combined to provide adequate power. To accomplish this, more cooperation between different disease-orientated research groups is needed. The Survivorship Taskforce of the EORTC is promoting this by stimulating collaborative projects which include data collection and analyses across different research groups. In some future research projects detailed information may be collected on possible risk factors and outcomes.

A more problematic aspect of the use of randomised trials for studying late effects is that, as they are not pre-specified trial end-points, they are often not reported in papers presenting trial results unless the findings are in some way remarkable. Consequently, systematic reviews that rely just on published information regarding late effects will tend to be able to present only information from studies with extreme results, with obvious consequences in terms of bias. This limitation can be overcome by carrying out a meta-analysis based on individual patient data, although such an approach is resource intensive as it is usually necessary to contact the original investigators of all the trials in a particular category, and

then collate centrally and check all the data that are forthcoming before it can be analysed.

Another limitation of data arising from randomised trials is that patients with substantial co-morbidities at the time of their cancer diagnosis are much less likely to be entered into randomised trials than patients who are otherwise healthy. This is likely to be the case even when such patients are not explicitly excluded in the trial protocol.

A final limitation applies particularly to studies in which the patients in one arm of the trial have been randomised to receive potentially cardiotoxic chemotherapy and patients in the other arm randomised not to receive it. In such trials it is often the case that the patients in the chemotherapy arm have their cardiac status more thoroughly assessed –both during treatment and during follow up- than do patients in the control arm. This may well introduce considerable bias into comparisons between the two trial arms for end-points other than mortality and in such cases meaningful analyses can only be carried out for cardiac mortality.

3.3. Observational studies

Another approach to obtaining information on the cardiac side-effects of cancer treatments is to obtain data from observational studies rather than randomised trials. Such studies can be informative, especially if they are population-based as, for example, studies based on large population-based cancer registries. Care is needed in their interpretation, however, as patients who are at increased risk of heart disease at the time when decisions on their treatment are made, will tend not to be given potentially cardiotoxic chemotherapy if it can possibly be avoided. Comparisons of subsequent heart disease rates in patients with and without such treatment may, therefore, provide misleading answers [56].

3.4. Achieving relevance for today's patients

Studies of the long-term cardiac effects of cancer treatments given in the past may not be immediately relevant to today's patients. One reason for this is that medical practice has changed with time. As mentioned before, modern radiation approach has significantly reduced normal tissue exposure. Also in systemic treatment changes have been implemented, for example, the cardiotoxicity of anthracyclines delivered today may be lower than previously due to changes in the way the drug is administered, e.g. by using continuous infusions rather than a bolus or by using a pegylated formulation. Careful consideration of these issues is therefore needed when interpreting any studies. A further issue is that baseline levels of cardiac mortality have decreased substantially over the last few decades in many countries, and levels of morbidity may have also changed, although such changes are generally less well documented than changes in mortality. This may mean that the absolute risk of late cardiac side-effects in patients treated today may differ from that for past populations of patients. Proportional increases in the incidence and mortality arising from the use of particular drugs are, however, usually reasonably stable across populations with different baseline rates.

The experience of the past can also be used to optimise future treatments as the data generated from patients treated in the past may provide dose–response information which can be used in mathematical models and thereby enable us to predict and compare long-term complications of present day treatment, thus guiding the choice of treatment in individual patients [57].

For newer treatments such as antibodies, small molecules, and highly conformal radiotherapy, observation time is still too short for reliable estimation of long-term complications. Vigilance and a strict safety-monitoring programme, even after approval of the drug, are essential.

Furthermore, we need uniform definitions of toxicity in order to allow proper comparison between studies.

3.5. Regulatory issues

For analysis of long-term complications from specific treatments we often need to be able to obtain data from different registries on particular, identifiable patients. Hence, ethical issues must be considered and approvals obtained. In some countries this may be more difficult than in others since there is a large variation in regulations concerning these issues.

Informed consent from all relevant patients may be virtually impossible to obtain retrospectively, since a proportion of patients will have died or their present address may not be known. Moreover, there may be ethical dilemmas when contacting patients treated many years ago who now consider themselves to be healthy. In most countries, permission to omit informed consent is possible in this situation. Another approach could be to incorporate upfront permission from patients entered into clinical trials on future outcomes.

3.6. Early detection of cardiac damage

Information on the possible value of measuring early subclinical damage using biomarkers and/or (functional) imaging following cardiotoxic chemotherapy [58–61] and radiation exposure of the heart [62] is still scarce.

3.6.1. Imaging
Cardiac imaging techniques such as 2D echocardiography or MUGA show clinically detectable left-ventricular dysfunction but earlier subclinical injury cannot be detected with these imaging modalities. Cardiac magnetic resonance imaging (MRI) may offer some possibilities in screening since it enables tissue characterisation and may lead to detection of diffuse interstitial fibrosis and changes in regional myocardial function. MRI also has disadvantages such as need for contrast, and its high cost and low availability. Newer imaging techniques, such as contrast and 3D echocardiography are also under investigation. These imaging modalities are expensive and should not be unnecessarily repeated. Therefore, screening guidelines need to be developed and optimal and cost-effective screening schedules evaluated.

3.6.2. Biomarkers
There are several cardiac biomarkers, such as troponin I (TnI), troponin T (TnT), B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP) and myeloperoxidase (MPO). There may

be a role for these biomarkers during follow-up to enable early detection of cardiac toxicity and possibly also during cancer therapy [63,64]. Circulating cardiac troponin (cTn, which can be TnI or TnT) is a sensitive and specific biomarker for detection of myocardial injury. Although most commonly used to detect myonecrosis in the setting of ischaemia, cTns are also elevated with other acute and chronic disease processes, including HF [65]. An increase in TnI level in patients undergoing chemotherapy may prove to be a useful means of detecting cardiotoxicity long before a reduction in left ventricular ejection fraction (LVEF) occurs and could allow for the selection of high-risk patients who could benefit from preventive treatment, such as treatment with angiotensin-converting enzyme (ACE) inhibitors and beta-blocking agents. In patients treated with trastuzumab, an increase in TnI level could help identifying those patients at risk for cardiotoxicity and unlikely to recover [66]. So far however, treatment is not adapted based on troponin levels.

Serum biomarkers may also be useful in helping diagnose asymptomatic left ventricular dysfunction or HF. Serum biomarkers such as brain natriuretic peptide (BNP) and N-terminal fragment (NT-proBNP) are most commonly used. However, there are limitations to BNP or NT-proBNP measurements, since other diseases may also cause abnormal BNP levels and serum levels also depend on other factors such as age. In a study analysing eight different biomarkers before start of treatment and every three months up to 15 months in patients treated with doxorubicin and trastuzumab, the risk of cardiotoxicity was especially related to an increase in TnI and MPO. The combination of both markers offered additive information about the risk of cardiotoxicity, but independent validation of these findings is necessary before application to clinical practice is possible [37]. Another study evaluating 200 patients with anthracycline-induced cardiomyopathy indicated that the percentage of responders to modern HF treatment decreased progressively as the time from the end of chemotherapy to the start of HF treatment increased [39].

Some biomarkers can also give quantitative information: the absolute value of these markers shortly after the administration of chemotherapy may indicate the degree of future left ventricular dysfunction.

At present there is no clear biomarker-set for CVD risk prediction during or after cancer treatment. Research is on-going regarding the predictive value and the ideal timing of biomarker measurements. Ideally, future research would validate a predictive set of tools to adapt treatment with respect to toxicity risk. Both biomarkers and imaging need further exploration in on-going trials. Early imaging, estimated CVD risk and the ability to associate toxicity with molecular profiling may lead to new recommendations for monitoring cancer patients during and after chemotherapy.

4.   Future guidelines

Although the increased risk of cardiac diseases following cancer therapy is well recognised, measures for primary and secondary prevention are still being developed.

Nowadays, cardiac monitoring is done during systemic treatment by serial measurements of left ventricular ejection fraction (LVEF). A decrease in LVEF reflects myocardial injury and the first sign of cardiac failure. Often during chemotherapy this cardiac dysfunction is reversible, and the LVEF decrease is only present at the moment of stress. By introduction of medication or rest, permanent dose reduction or cessation of chemotherapy treatment is not always necessary. What these moments of severe heart stress induce and the impact on cardiovascular risk during the rest of life are not well documented.

Recently, some evidence supports the use of other echocardiographic indices and biomarkers for the earlier detection of cardiac injury before a decrease in LVEF is noticed [67–71]. New imaging tools and markers are sought for earlier detection of serious cardiovascular morbidity partly to enable preventive measures, but also to spare low risk patients from unnecessary monitoring [72,73].

Currently there are no indications that the management of cancer treatment related cardiac diseases should differ from that due to other causes. In patients with (subclinical) HF treatment generally focuses on correcting underlying physiological abnormalities such as increased afterload and decreased contractility, and frequently includes treatment with angiotensin-converting enzyme (ACE) inhibitors and/or beta-blockers [74]. Several guidelines developed for treating patients with asymptomatic left ventricular dysfunction or HF (not specifically after cancer treatment) include e.g. beta-blockers, ACE-inhibitors and diuretics [75].

At this moment, in Europe formal guidelines exist only following antibody treatment (e.g. echocardiograms every three months) [76]. More data on incidence and reversibility, but moreover earlier indicators of cardiac damage, might in the future enable the necessary level of surveillance to be individualised.

Although little is formalised on cardiac surveillance following cancer treatment, it is clear that hypertension, shortness of breath or chronic fatigue need to be taken very seriously in cancer survivors. The risk of late cancer treatment related cardiotoxicity is often forgotten or underestimated, especially in women. Guidelines and educational sessions for general practitioners and other caregivers are needed to explain late cardiac risks and to better anticipate on late effects after cancer treatment [77,78].

Lifestyle factors such as smoking, obesity and lack of exercise and familial predisposition are important risk factors in CVD. Only a few studies have addressed whether factors such as these may modify the risk of treatment-related CVD [51]. Our knowledge of modifying effects of lifestyle and genetic predisposition on treatment-associated cardiovascular risk is only beginning to evolve. International collaborative studies are needed, including large numbers of survivors for whom not only treatment data but also detailed high-quality data on medical history, lifestyle, environmental, and occupational factors are available. The sequence of exposure to treatment and other risk factors deserves investigation, particularly for designing interventions where the treatments interact with modifiable risk factors. International pooling of data already available and data from new studies is essential to obtain sufficient power for interaction analyses allowing discrimination between additive, multiplicative and more than multiplicative effects of treatment and other cancer risk factors. Late effects

research should combine different outcomes like cardiovascular disease, second malignancies, early menopause, infertility etc., to obtain more detailed information on host (genetic sensitivity, life style, age etc.) and treatment (dose, type, timing, interactions etc.) factors. Also the quality of life and psycho-socio-economic impact should be taken into account, having possibly a direct (stress) or in-direct (access to care) influence on morbidity and mortality of various late effects.

Lifestyle interventions, exercise promotion and special care plans are proposed in cancer survivors. Whether all patients will benefit from these measures is uncertain. A risk based strategy is needed and long-term follow-up is essential [51,79–81].

5.   Conclusion

Extensive knowledge has already been gained from the past concerning cancer treatment related cardiotoxicity, but there is much more that can be done, although medical practice continues to evolve and so the resulting data need to be interpreted with care. Better knowledge is needed of the late effects of modern systemic treatments and of radiotherapy on critical structures of the heart and of possible interactions between treatment modalities. This knowledge will contribute to a longer life expectancy and better quality of life of cancer survivors, with less treatment-related morbidity from other diseases. Finally, prediction models taking into account the full spectrum of late effects are needed to guide primary treatment choice and appropriate follow up after cancer treatment.

Conflict of interest statement

Maja V. Maraldo were reported by: Berthe M.P. Aleman, Elizabeth C. Moser, Conny Vrieling, Sarah C. Darby.

Thomas M. Suter: Participation in a company sponsored speaker's bureau: Roche, Robopharmn, Novartis.

Lena Specht: Receipt of grants/research supports: Merck Serono – Receipt of honoraria or consultation fees: Takeda, Boehringer Ingelheim, Fresenius biotech – Participation in a company sponsored speaker's bureau: Takeda.

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