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Review Article

Dose constraints in breast cancer radiotherapy. A critical review

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ABSTRACT

Radiotherapy plays an essential role in the treatment of breast cancer (BC). Recent advances in treatment technology and radiobiological knowledge have a major impact in BC patients with locoregional disease as the majority are now long-term survivors.

Over the last three decades, intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) and deep inspiration breath-hold (DIBH) techniques, together with the increasing adoption of moderately hypofractionated and ultra-hypofractionated treatment schedules as well as the possibility to offer partial breast radiotherapy to a well-defined patient subset have significantly changed radiotherapy for BC patients.

As dose-volume constraints (DVCs) have to be adapted to these new treatment paradigms we have reviewed available evidence-based data concerning dose-constraints for the main organs at risk (OARs) that apply to the treatment of whole breast/chest wall radiotherapy, whole breast/chest wall radiotherapy including regional nodal irradiation (RNI) and partial breast irradiation (PBI), for the most relevant fractionation schedules that have been introduced recently. This narrative review provides a comprehensive summary that may help to harmonize treatment planning strategies.

Introduction

In early breast cancer (BC) radiation therapy (RT) prevents local recurrence, reduces BC-related mortality, and improves overall survival (OS) [1,2]. In addition, recently published evidence also indicates that any recurrence and BC mortality are reduced by adjuvant nodal RT, even in case of only minimal axillary involvement [3]. Unfortunately, RT is associated with the risk of both acute (early) and delayed (late) toxicity to organs at risk (OARs), and every effort should be made to minimize these adverse events. Over the past few decades, technological advances as well as a deeper understanding of underlying radiobiology have significantly contributed to this goal [4].

Intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and deep inspiration breath-hold (DIBH) techniques [5–7], together with the increasing adoption of moderately hypofractionated or ultra-hypofractionated treatment schedules as well as partial breast irradiation (PBI) that also changes the volume paradigm, have significantly changed RT for BC [8]. This paradigm shift has prompted the necessity to adapt/redefine dose-volume constraints (DVCs) in BC-RT. While corrections to constraints for normofractionated treatments based on the linear-quadratic-model may serve as a first approximation to constraints for hypofractionated treatments, this review tries to identify the already available data and directs to study protocols that may serve as an informed estimate where no data are yet

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available.

Efforts to identify safe dose limits, however, have mainly concentrated on lungs and heart, while there remains a lack of specific recommendations for other OARs routinely exposed in locoregional treatments. In addition, most commonly used DVCs were derived from studies that used three-dimensional conformal RT (3DCRT) techniques. This makes their application challenging when employing more advanced delivery techniques. The aim of this review is therefore to report – in a comprehensive and synoptic fashion and including all available evidence regarding the whole spectrum of treatment paradigms – evidence-based data concerning DVCs for the main OARs in the treatment of breast and chest wall (CW) RT across all currently established fractionation and treatment paradigms such as whole breast irradiation (WBI), locoregional treatments including regional nodal irradiation (RNI) and, finally, PBI. The contribution of boost to OARs dose is limited. Nevertheless, the recommended tolerance doses apply to WBI or WBI plus boost.

Literature overview of organ specific toxicity and resulting recommendations regarding DVCs for WBI with or without RNI

Lung toxicity and DVCs for lung

Lung tissue is relatively sensitive to radiation and the risk of lung toxicity remains a dose limiting factor in a variety of clinical situations. Radiation-induced lung damage involves resident and immune cells together with the activation of a cascade of pro-inflammatory cytokines and chemokines [9]. Radiation-induced pulmonary toxicity has four different clinically relevant manifestations that potentially compromise quality of life, radiation pneumonitis (RP), radiation fibrosis (RF), bronchiolitis obliterans organizing pneumonia (BOOP) as a rare and etiologically complex entity and, finally, second cancer risk as a potential stochastic complication. RP is an early inflammatory reaction (within one to three months after RT). RF is a late and irreversible event due to fibroblast proliferation and the accumulation of collagen in the interstitial pulmonary space and occurs 6–12 months after RT [10].

Literature data reported an overall incidence of clinical RP varying from 0.7 % to 14 % [11–13]. The incidence rate of RP seems to vary according to treatment schedule (total dose and dose per fraction), irradiated volume, type of radiation and RT technique. In addition, patient-specific factors (such as age, comorbidity, Body Mass Index (BMI)) and treatment-related factors (such as the association of systemic therapy, including endocrine therapy) can influence and increase lung toxicity [14].

Regarding RF after BC RT, few data are available in the literature. Previous studies with small samples of BC patients, found endocrine treatment with tamoxifen and dose to ipsilateral lung as predictors for RF [15]. More recently, Karlsen et al. published an interesting 12-year analysis on long-term pulmonary toxicity in 250 BCE patients receiving post-operative RT. They showed that chemotherapy and locoregional RT affected performance in pulmonary function tests (PFTs), but they failed to find any association between this decline in PFTs and long-term RF or patient-reported dyspnea [16]. An inflammatory lung disorder of the distal airways extending into the alveolar ducts and alveoli, has to be mentioned as a separate entity, called BOOP [14]. RT-BOOP syndrome is recognized as an indirect lung injury related to an autoimmune process [15]. An incidence of BOOP in BC patients after breast conserving therapy ranging from 1.8 % to 2.9 % has been reported [16]. Most of these patients received traditional WBI with conventional opposing tangential fields. The mechanism of development of BOOP is currently unknown, but the subpleural localization of the initial injury and the low doses received by directly adjacent lung tissue could be involved in its onset [17]. Based on this hypothesis, the increasing use of IMRT in BC patients may reduce the incidence of BOOP varying the dose distribution but there is no clinical robust evidence yet to support this theory.

Finally, lung exposure has also been associated with an increase in lung cancer incidence even with modern RT techniques. The risk of second primary lung cancer increases with lung dose (i.e. mean whole lung dose (MLD)). A case control study including more than 20.000 BCE patients reported that the relative risk (RR) of lung cancer after breast RT increased linearly with whole lung MLD at 8.5 % per Gy [18], with an even higher excess rate of 17.3 % per Gy for smokers. As RT is moving from tangents to more complex techniques it is not yet clear what component of the dose spectrum is most relevant to second cancer (SC) incidence and to what extent modern treatment techniques such as IMRT/VMAT or particle therapy may modulate these data for patients with significant lung exposure (see also paragraph 4 for in-depth discussion), especially because of several confounding factors such as a small number of events being detected with difficulties in collecting long-term follow-up data and the unclear effects of other elements (chemo-endocrine therapy, genetic predisposition or smoking habit) [19,20]. However, the results from an individual patient data *meta*-analyses of 40,781 women enrolled in 75 randomized clinical trials (BC RT versus no RT) documented an estimated absolute risk for second primary lung cancer of 4 % for long-term smokers and 0.3 % for nonsmokers and ex-smokers, showing a significant reduction of RT risk through smoking cessation [20].

Dose effect relationship data for all manifestations of pulmonary toxicity potentially caused by radiation are well studied for some of these manifestations and less well studied for others. Among the best studied (and also most relevant) endpoints are certainly Radiation Pneumonitis and Lung Fibrosis. As for BOOP as a rare manifestation no dose-volume-relationship has been established and as for SC induction the ALARA (As Low As Reasonably Achievable) principle applies, the recommended lung DVH constraints can mainly be deducted from datasets regarding RP and RF incidence. Different dosimetric parameters (Volume receiving 5 Gy, 10 Gy, 13 Gy, 20 Gy (V5Gy, V10Gy, V13Gy, V20Gy) and MLD) have usually been analysed retrospectively to evaluate their impact on RP risk. Two of these parameters, V20Gy and MLD, have then been mainly used clinically as simple and relatively robust predictors of RP risk [21–24], as the incidence of RP rises significantly at V20Gy $>$ 30 % of the ipsilateral lung volume [25] and/or at MLD values $>$ 10 Gy [26]. A systematic review of lung doses from BC-RT studies published during 2010–2015 found that mean ipsilateral lung dose (MLDipsi) was 9 Gy on average, and increased with the complexity of treatment as follows: 8.4 Gy per whole breast/CW irradiation in supine position without breathing control, 11.2 Gy when axilla/supraclavicular regions were included, 14 Gy when ipsilateral internal mammary chain (IMC) was also irradiated. DIBH treatment reduced MLDipsi by 1 Gy, 2 Gy, and 3 Gy, respectively. The use of IMRT seemed to be able to reduce MLDipsi when the target was more extensive such as with IMC irradiation, but it increased controlateral lung dose. The lowest MLDipsi was obtained with proton therapy or with treatment in prone or lateral decubital positioning [27]. Table 1 summarizes the most relevant lung DVCs based on literature data and international guidelines and recommendations. Regarding Whole Breast/Chest Wall (WB/CW) irradiation, in 2013, the Danish Breast Cancer Group (DBCG) [28] guidelines proposed V20Gy $\leq$ 25 % and V17Gy $\leq$ 25 % as ipsilateral lung DVC for the conventional fractionation schedule and the hypofractionation, respectively. These DVCs were used in the DBCG HYPO trial, a randomized phase III study to compare hypofractionated versus standard fractionated RT in 1882 patients with node-negative BC. At a median follow up of 7 years, no patients were hospitalized with radiation pneumonitis and no other lung toxicities were reported, we therefore suggest using the DVCs adopted by the authors [29] as they may be considered sufficiently robust and conservative. Several years later, the American Society for Radiation Oncology (ASTRO) [30] published guidelines for RT in early BC and recommended a more restrictive V20Gy $\leq$ 15 % and V16Gy $\leq$ 15 % (ipsilateral lung DVC) as ideal (and $<$ 20 % as acceptable) for the conventional fractionation schedule and hypofractionation, respectively, as defined in the ongoing trial RTOG 1005, a study comparing

Table 1
Lung dose constraints.

Organ at Risk	Conventional fractionation (2 Gy/fr)		Moderate hypofractionation (2.6–3.2 Gy/fr)		Ultra hypofractionation (5.2 Gy/fr)	
Ipsilateral Lung	*Breast/chest wall* MLD ≤ 8 Gy (range 7.9 3DCRT – 9.4 IMRT) [27]	*Systematic review*	*Breast/chest wall* V_{20Gy} < 10 % ([33,34] – VMAT treatment)	*Phase II Trial*	V_{8Gy} < 15 % [35]	*Phase III Trial*
	V_{10Gy} ≤ 35 % (acceptable < 40 %) [31]	*RTOG 1005*	V_{17Gy} ≤ 25 % [28,29]	*DBCG guidelines and trial protocol (Hypo trial)*		
	V_{5Gy} ≤ 50 % (acceptable < 55 %) [31]	*DBCG guidelines and trial protocol (Hypo trial)*	V_{8Gy} ≤ 35 % (acceptable < 40 %) [31]	*RTOG 1005*		
	V_{20Gy} < 25 % [28,29]	*DBCG guidelines, RTOG 1304, Alliance A221505*	V_{4Gy} ≤ 50 % (acceptable < 55 %) [31]	*Trial protocol (Hypo trial)*		
	Breast/chest wall and RLN	*SKAGEN trial*	MLD < 10–16 Gy ([29,33,34] – VMAT treatment)	*Phase II Trial*		
	V_{20Gy} ≤ 35 % [28,36,38,39]	*Alliance A221505*	*Breast/chest wall and RLN*	*RTOG 1304*		
	V_{10Gy} ≤ 65 % [38]	*DBCG guidelines*	V_{18Gy} ≤ 35 % [36]	*SKAGEN trial*		
	V_{5Gy} ≤ 75 % [38]	*SKAGEN trial*	V_{17Gy} ≤ 35 % [39]			
	MLD ≤ 18 Gy [28,39] (range 14I MRT-20 3DCRT) [27]	*Systematic review*				
Contralateral Lung	*Breast/chest wall* V_{5Gy} ≤ 10 % (acceptable < 15 %) [21,31,36,38]	*QUANTEC, RTOG 1005, RTOG 1304, Alliance A221505*	*Breast/chest wall* V_{4Gy} ≤ 10 % (acceptable < 15 %) [30,31]	*ASTRO guidelines, RTOG 1005*	Not available	
	Breast/chest wall and RLN V_{5Gy} ≤ 15 % [36]	*RTOG 1304*	*Breast/chest wall and RLN* $V_{4.8Gy}$ ≤ 10 % (acceptable < 15 %) [38]	*Alliance A221505*		
Lungs	*Breast/chest wall* MLD ≤ 6 Gy [27]	*Systematic review*	Not available		Not available	

MLD: mean lung dose; 3DCRT: three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiotherapy; RLN: regional lymph nodes. Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

conventional or hypofractionated WBI plus sequential boost vs moderately hypofractionated WBI with simultaneous integrated boost. Preliminary results based on 2262 enrolled patients were presented at ASTRO's 64th Annual Meeting and the authors reported low rates of ≥ grade 3 treatment-related adverse effects (AEs) (without providing further details) regardless of fractionation regimen [31]. They allowed the use of IMRT in the protocol, thus including constraint tradeoffs to optimize ipsilateral lung low dose exposure (V10Gy and V5Gy), that could be very useful in the era of more advanced delivery techniques. Another interesting clinical dataset that might be considered to refine constraints comes from an Italian mono-institutional study: a large cohort of BC patients treated with hypofractionated VMAT-based treatments. Only 2 cases of G2 RP were reported in the long-term analysis including 450 patients with a median follow-up of 6 years [32]. They observed cutoff values that may be used as reasonable constraints for ipsilateral lung of V20Gy < 10 % and MLD < 10 Gy [33,34]. Finally, reliable DVCs for ultra-hypofractionated schedules are derived only from the Fast-Forward trial [35], a multicenter, randomized, non-inferiority, phase III trial, comparing an adjuvant RT 5-fraction schedule (26–27 Gy/5 fractions) with a 15-fraction scheme and including a total of 4096 patients. The protocol ipsilateral lung DVC was V8Gy < 15 % and the treatment was delivered with 3DCRT. At a median follow up of 5 years, the authors reported a very low incidence of symptomatic lung fibrosis. Excluding the Italian mono-institutional study on VMAT-based treatment, all of these sources allowed the use of both 3DCRT and IMRT, without differences in terms of DVCs based on the employed technique. Regarding WB/CW RT including RNI, few data from completed studies are available, thus, for a conventional fractionation schedule, we suggest referring to the ipsilateral lung DVC (V20Gy ≤ 35 %) recommended in the previously mentioned DBCG guidelines [28] (despite ASTRO guidelines that focused only on WBRT) and to the requirements in the ongoing RTOG 1304 trial (V10Gy ≤ 65 % and V5Gy ≤ 75 %), a phase III study to determine if WB/CW and RNI reduces invasive breast cancer recurrence free interval in BC patients with positive axillary nodes who are ypN0 after neoadjuvant chemotherapy [36]. Preliminary results on 1556 evaluable patients were presented at the 2023 San Antonio Breast Cancer Symposium. The authors reported no unexpected toxicities. Grade 4 toxicities were rare and the rate of grade 3 toxicities was 6.5 % with no regional nodal irradiation and 10 % with regional nodal irradiation (radiation dermatitits was the most common toxicity, no further details were provided). [37]. For hypofractionation, DBCG guidelines did not define lung DVCs, thus we suggest referring to the ipsilateral lung DVCs defined in the ongoing trials Alliance A221505 (a phase III randomized trial of hypofractionated versus conventional fractionation post mastectomy RT in BC patients with breast reconstruction) and SKAGEN (a randomized trial to investigate the morbidities following normofractionated versus moderately hypofractionated loco-regional RT in patients with early breast cancer and an indication for RNI) as a reasonable option [38,39].

Heart toxicity and DVCs for heart

Several studies demonstrated that RT is an independent risk factor for cardiovascular disease (CVD) more than 10 years after BC-RT [40–42].

RT, in the acute phase, causes endothelial damage and induces activation of the inflammatory cytokine cascade, and this leads over time to activation of all known components of the fibrosis response, such as fibroblasts, TGF-beta cascade and extracellular matrix remodelling (chronic phase) [43–45]. Endothelial cells are sensitive to radiation and doses ≥ 2 Gy induce expression of inflammatory adhesion molecules and promote leukocyte adhesion [46].

Coronary artery disease is among the most common cardiac complications related to RT [47]. Several studies reported that patients who underwent RT have a 10-year risk of 5–10 % of developing coronary artery disease [48]. Ionizing radiation, however, can also cause fibrosis, retraction and calcification of the valve tissue resulting in both regurgitation and stenosis [49]. RT can also induce direct damage of myocytes and promote myocardial fibrosis, resulting in diastolic dysfunction (heart failure with preserved ejection fraction) or, rarely, restrictive cardiomyopathy [50]. Finally, RT can provoke pericardial damage leading to acute and chronic pericarditis and conduction system injuries

leading to several rhythm disorders [51]. McGale, analyzing a cohort of 35.000 women treated between 1976 and 2006, reported a higher risk of pericarditis (RR: 1.61) and valvular heart disease (RR: 1.54) in left-sided than in right-sided irradiated BC [49].

To define dose constraints, the correlation between the dose received by an OAR and the occurrence of side effects has to be analyzed. However, confounding factors (other factors affecting cardiac risk) and the long latency of cardiac side effects makes this evaluation difficult. In addition, the development of new RT techniques amplifies this difficulty.

Darby et al. reported a dose–effect relationship between risk of cardiac side effects and mean heart dose (MHD), and a dose–effect relationship between cardiac toxicity and dose to the left anterior descending (LAD) artery was observed by Zureick et al. [41,52]. The study by Darby et colleagues demonstrated a direct correlation between MHD and the risk of major coronary events, with a linear increase in observed risk, reporting a 7.4 % increased risk every additional 1 Gy.

Zureick et al suggested that LAD EQD2 Dmax higher than 6.7 Gy correlated with adverse cardiac events. However, these studies had several limitations: the analyses were retrospective, were lacking individual dosimetry and the analyzed patients were treated from the early 1970 s to the 2000 s, and dose-volume relationships were therefore only applicable to the standard RT techniques used in this period that were mainly consisting of basic tangent-based techniques.

Avoiding the clinical consequences of cardiac exposure by using MHD as the only constraint is likely not sufficient. In the BACCARAT trial, the authors showed that limiting MHD alone may result in excessive irradiation of certain cardiac substructures as the predictive value of MHD for the exposure of single cardiac substructures, including coronary arteries, is not reliable [53]. Nilsson et al. retrospectively analyzed 200 irradiated patients, all of whom underwent coronarography after RT, showing a direct correlation between high dose hotspots and the location of coronary stenosis [54].

Most of the studies on correlation between OAR dose and occurrence of side effects included only patients who received 3DCRT and **conventional fractionation**. The following reports are the most relevant regarding this issue. Van den Bogaard et al. performed an individual Computerized Tomography (CT)-based RT plan analysis to validate the Darby model and to investigate if other dose-distribution parameters are predictive of CVD [55]. A total of 910 patients were included in this study and 30 patients (3.3 %) developed acute CVD during follow-up. An increase of the cumulative incidence of acute coronary events by 16.5 % per Gy was found, but the left ventricle (LV) V5Gy was the most important prognostic DVC (V5Gy $<$ 17 %). Erven et al., using the ecographic strain-rate imaging method, analyzed early radiation-induced changes in the function of 18 separate segments of the LV [56]. Analysing 30 patients, they showed a significant decrease in systolic myocardial deformation in the apical segments receiving $>$ 3 Gy vs. $<$ 3 Gy. Skyttä et al. prospectively investigated the relationship between cardiac doses and the serum biomarker troponin T (TnT) on a total of 58 patients with early stage left-sided BC treated with adjuvant RT without prior chemotherapy (CT). [57]. TnT increased during RT from baseline in 12/58 patients (21 %) and the authors found a significant correlation between the increase of TnT and MHD and mean LV dose (4 vs. 2.8 Gy and 6.7 vs. 4.5 Gy). Similar results were also observed for other dosimetric parameters like V15Gy (58.6 vs. 40 %) and V20Gy (55.4 vs. 36.2 %) of the LAD, V5Gy (12 vs. 8.1 %), V10Gy (8.4 vs. 4.9 %), V15Gy (7.1 vs. 4 %) and V20Gy (5.7 vs. 3.5 %) of the heart and V5Gy (22 vs. 14.5 %), V10Gy (15.5 vs. 8.6 %), V15Gy (13.2 vs. 7.2 %) and V20Gy (11.1 vs. 6.2 %) of the LV. Beaton et al. analyzed treatment planning parameters in 5249 patients who underwent RT 10 years earlier, comparing 76 patients who died of CVD (cases) to a matched population of 150 patients who did not (controls) [58]. They performed an individual CT-based RT plan evaluation. They found a higher proportion of cases than controls with CVD risk factors and lower cardiac RT doses, suggesting that radiation oncologists had deliberately spared the heart when patients presented with CVD risk factors. It was observed that 75 % of patients without cardiac toxicity had received a MHD and Dmax LAD ($EQD2_3$ Gy) of no more than 3.3 Gy and 45.4 Gy, respectively, and that in 80 % of these patients heart V25Gy was $<$ 5 %. They therefore concluded that the risk of radiation induced cardiac death at 10-years appears to be very low if these limits are respected and recommended those as clinically useful dose constraints.

In conclusion, it is well documented that a reduction of MHD is associated with lower risks of cardiac late effects in a predominantly tangential 3DCRT setting. The use of modern techniques for WBI allows to achieve very low MHDs, but if only MHD is used as a dose constraint, subvolumes such as the heart apex or parts of the LAD can be exposed to much higher doses [59]. It is therefore very likely crucial to use additional dose limits in addition to MHD in the future, as it is already common practice in present clinical studies (see below and what is considered in the discussion).

Based on the dosimetric data discussed above, some scientific societies, such as DEGRO [60], published recommendations for cardiac dose constraints for conventional fractionation RT.

More recently, DVCs suggestions have also been made for **hypofractionation** [29,61], while for ultrahypofractionation data regarding late cardiac toxicities are still elusive.

The authors of the DBCG HYPO trial for patients enrolled in the hypofractionation arm defined the dose constraints for heart as V17Gy $\leq$ 10 % and V35Gy $\leq$ 5 %. The contouring of LAD was optional, and if LAD was delineated, the required dose constraint was Dmax $<$ 17 Gy. In a quality assessment of the treatment plans (3DCRT with Field-In-Field, IMRT was also allowed) they found that the compliance for heart constraints was superior than 99 %, although a high number of missing data was registered for the optional LAD contouring [29]. As very few cardiovascular events (5 cardiac deaths) were registered in the enrolled patients after a median follow-up of 7.3 years, with no indication of an excess risk, they concluded that the 95th percentile values for heart dosimetric parameters could be suggested as clinically useful constraints for the broad application in whole-breast RT planning not including regional lymphnodes (V17Gy $\leq$ 5 % and V35Gy $\leq$ 1 % for hypofractionation and V20Gy $\leq$ 5 % and V40Gy $\leq$ 1 % for standard fractionation). Extrapolating from these data by simply relaxing those constraints slightly (not based on a dedicated dataset acquired for this paradigm), they suggested a heart V17Gy $<$ 10 % and V35Gy $<$ 5 % (for hypofractionation) and V20Gy $<$ 10 % and V40Gy $<$ 5 % (for standard fractionation) for locoregional treatments including lymphnodes [29]. Franceschini et al. investigated the use of hypofractionated RT with concomitant boost delivered with VMAT in patients with early-stage BC who underwent conservative surgery [32]. The heart dose constraints suggested were V40Gy $<$ 3 % and V18Gy $<$ 5 %. At 2-year follow-up no symptomatic heart toxicities were recorded. These constraints are less restrictive than the previous ones, therefore, they should be considered rigorously if the constraints proposed in the HYPO trial cannot be met. No constraints for MHD were defined in these two studies. In RTOG 1005 it was required that MHD did not exceed 3.2 Gy (with 4 Gy being still acceptable), but no heart toxicity data were published [31]. Also, for **ultrahypofractionated treatments**, long term cardiac toxicity data are not available and orientation in this setting is only provided by study protocol DVC requirements. In the Fast Forward trial 3DCRT with tangential field arrangements was used and protocol dose constraints for the heart were V1.5 Gy $<$ 30 % and V7Gy $<$ 5 %. In the 5-years analysis, 27 patients out of 4096 enrolled died because of cardiac events (10 in the moderately hypofractionated arm, 17 in the 5-fraction arms). Though the low number of events and the short follow-up do not allow correlations between dosimetric parameters and major cardiac events, the protocol requirements may serve as a reasonable suggestion for clinically applicable DVCs in the ultrahypofractionation setting [35].

Based on all these data, in Table 2 we summarize the most relevant heart and cardiac substructure dose constraints.

DVCs for contralateral breast

While dose to the contralateral breast (CB) in all types of modern primary breast RT is of little relevance for deterministic acute or late side effects, it is nevertheless of major concern due to the risk of potential cancer induction [62]. This endpoint is related to the stochastic effects of ionizing radiation [63]. A Surveillance, Epidemiology, and End Results (SEER) database reported an absolute increase of CB cancer risk associated with RT of 0.5 %, 1.3 %, and 1.6 % (10–15-and 20-year actuarial rates, respectively [64]). Young women are most significantly at-risk. The WECARE study observed that patients < 40 years of age who received > 1 Gy of absorbed dose to the CB had a 2.5-fold greater risk for CB cancer than unexposed women (RR = 2.5; 95 % CI 1.4–4.5) [65]. Hooning et al. reported a linear excess RR of 0.21 per Gy increase in patients younger than 45 years. The relationship was stronger for the risk of medially located contralateral tumours (linear excess RR/Gy 0.37) [66].

Based on these relatively clear data, international guidelines and national recommendations suggest giving the lowest possible dose to the CB, both for conventional (25 fractions) and hypofractionated (15 fractions) schedules [29,30,67]. As dose trade-offs have to be made with target coverage and other relevant OARs these trade-offs have to be chosen, and estimating lifetime consequences of heart, lung and CB exposure, Thomsen et al. concluded that CB exposure was of lesser priority than dose coverage or heart and lung constraints [29]. There are no studies reporting a direct relationship between specific dose constraints and the incidence of SC in the CB. As a result, dose limits are derived from ongoing clinical trials, however, it should be noted that these constraints are too strict, especially when all other benefits of non-3DCRT (IMRT/VMAT) such as heart sparing are to be maximized. Regarding **conventional fractionation**, RTOG1005 [31] and Alliance 221,505 [38] allowed the use of either 3DCRT or IMRT with no distinction for dose limits. The only difference between studies concerned RNI, as it was included in the Alliance (RNI +) but not in the RTOG1005 (RNI-) trial. Dose constraints are D5%≤1.86 (RNI-) and D10%≤3Gy (RNI +). In a recent overview of involved site RT in adult lymphomas the authors suggested that the volume receiving > 4 Gy should be below 10 % and Dmean should be < 4 Gy [68] which seems reasonable also for BC. For **hypofractionated** (15 fractions) schedules, both the RTOG1055 and Alliance221505 trials used a dose constraint of D5%≤1.44 Gy for hypofractionation, regardless of RNI, with no variations in delivery technique. De Rose et al. evaluated 2-year toxicity and cosmesis in patients with early stage BC treated with 3 week/15 fraction hypofractionated SIB-VMAT to the whole breast (40.5 Gy) and tumour bed (48 Gy) [34]. In their study the constraint for CB was a mean dose < 3 Gy.

In conclusion, as stochastic effects of ionizing radiation induce second tumours, it is fundamental to expose the CB to the lowest dose possible, especially in young patients [63,66,69]. A set of commonly used constraints are reported in Table 3, but for this endpoint it is hard to identify a reliably validated dose limit due to the lack of data as a consequence of the necessary long follow up and a lack of patient individual dosimetric data [67]. Particularly for modern paradigms such as PBI and IMRT/VMAT, no reliable clinical data are yet available and assumptions have to be made in clinical decision making (see also paragraph 4).

Brachial plexus toxicity and DVCs for brachial plexus

Brachial plexus neuropathy (BPN) is a potential late toxicity following surgery and/or radiation for BC, supraclavicular (SCLNs) and/or axillary (ALN) lymphnode targets. Clinical symptoms of BPN are neuropathic pain, paresthesia or motor weakness of the upper extremities, and can cause significant morbidity [70]. The brachial plexus (BP) appears to be especially sensitive to variations in fractionation schedule, with the risk of injury being much higher for larger fractions despite equivalent BED [71]. Emami et al. suggested that the TD 5/5 to the entire BP was 60 Gy for normofractionation [72] and in a recent update the risk of clinically observed radiation induced BPN (RIBPN) seems to be < 5 % with standard fractionation after 5 years of completing RT, when the dose tolerance is limited to 60 Gy [73]. Nevertheless, with the prevalence of 3DCRT in studies so far and an increasing use of hypofractionated RT recently, toxicity to BP needs to be reevaluated as there are insufficient data regarding the incidence of BPN after RT with new radiation techniques [74,75] and as fractionation seems to dramatically modulate tolerance doses. A review showed that the use of doses per fraction in the range from 2.2 Gy to 4.58 Gy with total doses between 43.5 Gy and 60 Gy causes a significant risk of BPN which ranges from 1.7 % to up to 73 % [76]. The risk of RIBPN was smaller than 1 % for doses between 2.2 and 2.5 Gy with the total dose ranging between 34 and 40 Gy. Regarding the influence of treatment technique on the toxicity of OARs only a limited experience has been reported in the literature [77–79]. Prospective studies are needed to investigate DVCs in a more detailed fashion to improve the reliability of BP dose constraints and the plethora of factors that may modify RIBPN risk. Surgical manipulation of the axilla and CT have to be taken into account as additional factors which may increase the risk of RIBPN [80–82]. Regarding **conventional fractionation** the DBCG recommends that the maximum dose to the BP should not exceed 54 Gy [28] which is a reasonable suggestion given the available data.

A systematic review and *meta*-analysis by Yan et al. reported a significant increase in RIBPN risk for each Gy increase in brachial plexus maximum dose (BPD_{max}) (RR, 1.11; 95 % CI 1.07–1.15) and suggested that current BP constraints of 60–66 Gy for conventional fractionation are safe [83]. Lundstedt et al. reported the incidence of paresthesia in 192 patients treated with RT on SCLN lymphonodes. BP was contoured modifying guidelines published by Hall et al. [84]. Paresthesia was reported in 25 % of patients when BP V40Gy was > 13.5 cm^3 [85]. In a study of Jin et al, 156 patients received 50 Gy in 25 fractions and a boost to involved nodes and were compared with a control group of 297 patients treated with supraclavicular irradiation without boost. Dosimetric data were available in 74 patients in the first group and in 126 in the control group. BP was contoured following guidelines by Hall and colleagues. V50Gy > 90 % (33.3 % in V50Gy < 90 % and 63.6 % in V50Gy > 90 %) tended to develop more BPN related symptoms (p = 0.07) [86]. In these last two retrospective studies [85,86] patients were treated with 3DCRT in the first one and with 3DCRT (25 patients)/IMRT (127 patients) in the second one, respectively.

Regarding **hypofractionated RT** in line with the data reported above and serving as a reasonable synoptic recommendation DBCG guidelines for the Skagen 1 trial therefore require maximum dose to BP to remain below 46.25 Gy [39]. BP dose constraints reported in the literature are summarized in Table 4.

DVCs for humeral head

The effect of radiation doses received by the humeral heads during locoregional breast RT, including lymphnode areas, has not been well investigated. Data regarding doses received by the humeral head and adjacent tissues in RT for BC are scarce and there is no reported dose–effect relationship for shoulder mobility [89]. European Society for Radiotherapy and Oncology (ESTRO) guidelines suggest adding an expansion of 1 cm around the anatomical humeral head to obtain a planning risk volume (PRV), but no specific dose constraints are recommended [90].

In a recent publication Belaidi et al. reported data on 159 BCE patients receiving locoregional treatment with Helical Tomotherapy. To our knowledge this is the first study that correlated dosimetric parameters of the humeral head with late toxicity. After a median follow-up of 48 months the authors observed a very low rate of clinical adverse events [proximal humerus fracture (0.6 %), shoulder pain (3.8 %) and functional limitations (1.9 %)] without any significant difference in the

Table 2
Heart and cardiac substructure dose constraints.

Organ at risk	Conventional fractionation (2 Gy/fr)		Moderate hypofractionation (2.6–3.2 Gy/fr)		Ultra hypofractionation (5.2 Gy/fr)	
Heart	*Breast/chest wall* $V_{20Gy} \leq 5$ % [31,61] $V_{40Gy} \leq 1$ % [61] D_{mean} 2.5 Gy* (optimal) [57,60] $D_{mean} < 4$ Gy [31]	*Original scientific article, trial protocol (RTOG1005)* *Original scientific article, DEGRO guidelines, trial protocol (RTOG1005)*	*Breast/chest wall* $V_{17Gy} \leq 5$ % [61] $V_{35Gy} \leq 1$ % [61] $D_{mean} < 3.2$ Gy [31]	*Original scientific article, trial protocol (RTOG1005)*	$V_{7Gy} < 5$ % (3DCRT) [35] $V_{1.5Gy} < 30$ % (3DCRT) [35] Not available for IMRT and VMAT	*Original scientific article*
	Breast/chest wall and RLN $V_{20Gy} \leq 10$ % [61] $V_{40Gy} \leq 5$ % [61] $D_{mean} < 5$ Gy [36] *With DIBH	*Original scientific article, trial protocol (RTOG 1304)*	*Breast/chest wall and RLN* $V_{17Gy} \leq 10$ % [61] $V_{35Gy} \leq 5$ % [61]	*Original scientific article*		
LADCA	Dmax < 20 Gy [60] Dmax < 45 Gy*[58] Dmean < 10 Gy [29] V30Gy < 2 % [29] V40Gy < 1 % [29] * End-point: cardiac death; as, however, LAD-related and muscle-related toxicity cannot yet reliably be separated, as the dimension of both muscle and LAD is small, and as positioning of the anterior heart is not perfect, it seems prudent to keep maximum dose to the anterior heart − thus also dose to the LAD − in any case ≪ 30 Gy, in line with the published recommendations for anterior heart also reported in this table	*DEGRO guidelines, Original scientific article, Trial protocol (Hypo trial)*	$D_{max} < 17$ Gy [61]	*Original scientific article*		
LV	$D_{mean} < 3$ Gy [56] $D_{mean} < 4.5$ Gy [57] $V_{5Gy} < 17$ % [55] $V_{23Gy} < 5$ % [29]	*Original scientific articles, Trial protocol (Hypo trial)*				

LADCA: Left Anterior Descendent Coronary artery; LV: Left Ventricle; 3DCRT: three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiotherapy; VMAT: volumetric-modulated arc therapy; Dmax: Maximum dose; Dmean: Mean dose; RT: radiation-therapy. Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

Table 3
Contralateral Breast dose constraints.

Organ at risk	Conventional fractionation (2 Gy/fr)	Moderate hypofractionation (2.6–3.2 Gy/fr)	Ultra hypofractionation (5.2 Gy/fr)
Contralateral Breast	ALARA [30,61,67] $D_{5\%} \leq 1.86$ Gy (RNI −) [31,38] $D_{10\%} \leq 3$ Gy (RNI +) [31,38] $V_{4Gy} < 10$ % [68] $D_{mean} < 4$ Gy [68]	ALARA [30,61,67] $D_{5\%} \leq 1.44$ Gy (RNI −) [31,38] $D_{10\%} \leq 3$ Gy (RNI +) [31,38] $D_{mean} < 3$ Gy [34]	Not available

ALARA: As Low As Reasonably Achievable; D_{mean}: mean dose; D_{max}: Maximum dose; $D_{0.1cc}$: Dose to 0.1 cc of volume; RNI: regional nodes irradiation; Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

maximum and average doses between symptomatic and asymptomatic patients [89]. As a consequence of these inhomogeneous and incomplete datasets we currently have no robust clinical data to support specific DVCs for humeral heads.

Again, following the DBCG guidelines for the Skagen 1 trial seems reasonable in this context and we therefore suggest to reduce the dose to the humeral head to the necessary minimum and preferably to less than 50 % of prescription dose (Table 4) [39].

Esophageal toxicity and DVCs for esophagus

Symptomatic radiation esophagitis is an infrequent complication of radiation treatment for BC and usually occurs in those patients in whom SCLN irradiation is indicated [91].

Esophagus exposure, however, has also been associated with an increase in esophageal cancer incidence. A dose–response relationship based on 252 women who developed esophageal cancer after BC-RT suggests that the risk increases by 7.1 % per Gy median oesophagus dose [92]. A recent systematic review demonstrated that, for breast radiotherapy including lymphnodes, the average mean oesophagus dose is 11.4 Gy and this may nearly double oesophageal cancer risk [93]. Few studies have examined the incidence of esophagitis in patients undergoing treatment for BC and even fewer have assessed esophageal DVCs for **conventional fractionated** and **hypofractionated** RT. Yaney et al. conducted a single-institution retrospective study analyzing 531 BCE patients who underwent RNI with conventional fractionation using both 3DCRT or IMRT. Target volume delineation was based on the RTOG Breast Atlas for high-risk, node-positive breast cancers (e.g., T3–4, N2–3). The esophagus was retrospectively contoured from the caudal edge of the cricoid cartilage to the carina. Grade 2 esophagitis was 16.2 % (86/531) and was significantly higher in patients treated with IMRT versus 3DCRT ($p < 0.0001$). Mean esophageal dose, Dmax and V10Gy, V20Gy, V30Gy, V40Gy and V50Gy were significantly associated with grade 2 esophagitis. The identified dose cutoffs resulting in increased toxicity for esophageal Dmean, V10Gy and V20Gy were 11 Gy, 30 % and 15 %, respectively [87].

West et al. carried out a single-arm prospective observational study to determine dosimetric factors related to incidence and grade of

Table 4
Dose constraints for other OARs routinely involved in breast locoregional treatment.

Organ at risk	Conventional fractionation (2Gy/fr)	Moderate hypofractionation (2.6-2.9 Gy/fr)	Ultra hypofractionation (5.2 Gy/fr)
Brachial Plexus	Dmax ≤ 54 Gy [14] V_{40Gy} < 13.5cm^3 [85] V_{50Gy} < 90% [86]	Dmax 46.25 Gy [39]	Not available
Humeral Head	ALARA	ALARA	Not available
Esophagus	Dmean ≤ 11 Gy, V_{10Gy} ≤ 30%, V_{20Gy} ≤ 15%[87]ˆ ˆ(when contoured along the entire length) Dmean ≤ 31 Gy [88]° °(when contoured from the superior to the inferior border of the supraclavicular PTV)	V_{25Gy} < 20% and V_{35Gy} < 0,27 mL [89]* *(when contoured from the lower border level of the cricoid cartilage to the lower margin of the aortic arch)	Not available
Liver	Dmean ≤ 3 Gy (left breast) [90] Dmean ≤ 4 Gy (right breast) [90]	Dmean ≤ 3 Gy(left breast) , Dmean ≤ 4 Gy (right breast) [90]	Not available
Thyroid	V_{30Gy} < 50% [91] Dmean < 21 Gy [92]	Dmean < 21 Gy [93]	Not available
Chest Wall	D2cc ≤ 52 Gy [94]	D_{2cc} ≤ 52 Gy $_{EQD2}$ [94]	Not available
Spinal Cord	Dmax ≤ 45 Gy (optimal) [95] Dmax <50 Gy (mandatory) [95]	Dmax ≤ 37.8 Gy (optimal) [96] Dmax < 42 Gy (mandatory) [96]	Not available

ALARA: As Low As Reasonably Achievable; D_{mean}: mean dose; D_{max}: Maximum dose; Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

esophagitis in 77 BC patients receiving IMRT to the SCLNs. The planned dose was 50 Gy in 25 fractions. Esophagus was contoured from the superior to the inferior border of the supraclavicular planning target volume (PTV). There was a higher incidence of grade 2 esophagitis in patients receiving a mean oesophageal dose of > 31 Gy compared to those receiving < 31 Gy (18/34 versus 6/24, respectively, p = 0.025). There was also a difference in patients who had > 1 cm of pharynx included in supraclavicular fossa fields compared to those with < 1 cm (15/24 versus 9/24 respectively, p = 0.0116). The authors concluded that by limiting mean dose to the irradiated esophagus to < 31 Gy and ensuring that less than 1 cm of the pharynx is included in the supraclavicular field, the incidence of grade 2 esophagitis could be reduced [94].

Regarding **hypofractionated RT**, Wang et al. conducted one of the few prospective studies to investigate dosimetric predictors for radiation esophagitis in BC patients undergoing hypofractionated regional nodal radiotherapy [88]. All patients were irradiated to the CW, the supra-infraclavicular fossa and level II of the axilla with 43.5 Gy in 15 fractions over 3 weeks. RT was delivered with IMRT except that the CW was irradiated with an electron technique in a small subgroup of patients. Esophagus was contoured from the lower border level of the cricoid cartilage to the lower margin of the aortic arch. The incidence of grade 2 esophagitis was 40.9 % (122/298) and grade 3 was 0.3 % (1/298).

From this analysis V25Gy < 20 % and V35Gy < 0.27 ml emerged as dosimetric parameters linked to a decreased risk of grade 2 radiation esophagitis and these constraints seem reasonable to also reduce esophageal second cancer risk as much as possible. In Table 4 we summarize esophagus dose constraints for conventional and hypofractionated RT suggested by these studies.

Hepatic toxicity and DVCs for liver

Few studies have examined toxic effects of breast RT on the liver and its impact has remained unclear, given that, for most patients, liver exposure from RT for BC is low. RT-induced liver disease (RILD) is generally defined as a radiation hepatitis or a subacute form of liver injury as a consequence of radiation with a ≥ 2-fold increase in the level of alkaline phosphatase (ALP) (classic type) or ≥ 5-fold increase in the level of aspartate transaminase (AST)/alanine transferase (ALT) (non-classic type) following RT. Studies analyzing consequences of RT for liver malignancies suggest that the dose constraints for normal liver volumes are a D_{mean} ≤ 28–32 Gy in 2 Gy fractions to prevent RILD [95]. However, these dose constraints are unrealistically high considering the prescribed dose for BC and the limited anatomical vicinity/overlap of liver and breast/CW targets. Park et al. evaluated the early effect of radiation dose on liver function in 125 of 185 BCE patients undergoing VMAT [96]. In patients who underwent RT to the breast alone, dose prescription was 42.56 Gy in 16 fractions with a sequential boost of 10.64 Gy in 4 fractions; in patients who received RNI the dose was administered with conventional fractionation of 50 Gy in 25 fractions with a sequential boost of 10–14 Gy. In post-mastectomy patients a total dose of 50 Gy in 25 fractions was delivered to the CW and regional lymph nodes. The authors collected the results of liver function tests (LFR) including albumin, total and direct bilirubin, AST, ALT and ALP levels and registered DVCs such as mean dose and relative liver volume receiving 10 Gy, 20 Gy and 30 Gy. A total of 31 patients had liver function test results outside normal limits. No patients, however, had RILD. Based on all this data, both for **normo and hypofractionated RT**, keeping D_{mean} ≤ 3 Gy and ≤ 4 Gy for left and right BC, respectively, may be a useful dose objective that can be easily utilized for VMAT planning.

Liver dose constraints reported in the literature are summarized in Table 4.

Thyroid gland toxicity and DVCs for thyroid gland

A large number of studies have demonstrated that the thyroid gland is sensitive to radiation and its irradiation can cause disorders such as hypothyroidism (HT), Graves' disease, and thyroid cancer [72,97–99]. Unfortunately, knowledge of radiation-induced HT in BC patients is also limited because the thyroid gland is not routinely defined/contoured as an OAR. The few available studies have reported an HT incidence of 6 %–21 % [100–104]. Regarding **normofractionation,** a randomized pilot study was conducted by Tunio et al. Forty BC patients with baseline normal thyroid function tests were randomized into two groups: adjuvant CW/breast with SCLN RT and control group (adjuvant CW/breast) [105]. Patients were treated with 3DCRT. At 52 months, four patients (10 %) had HT. The study showed that the risk of HT in BC patients after SCLN RT depends on the thyroid gland volume and V30Gy < 50 % was identified as a clinically useful dose cutoff. Kanyılmaz et al. estimated, retrospectively, the incidence of HT after RT in 243 patients and evaluated its predictors, with a focus on radiation DVCs [106]. All patients received RT using 3DCRT with a field-In-field technique, in normofractionation, to the breast/CW and a single anterior field (or combined anterior and posterior fields) for SCLN. Of 243 patients, 51 (21 %) were diagnosed with HT, 22 (9.1 %) with clinical HT and 29 (11.9 %) with subclinical HT. They reported a D_{mean} > 21 Gy as the only factor that predicted HT. Regarding **hypofractionation**, only Zhao and colleagues evaluated the incidence of HT after RT with hypofractionation in 500 patients [107]. They observed a significant increase of 2-year cumulative incidence of HT comparing BC patients with and without SCLN irradiation (31.5 % and 11.4 %, p < 0.001) after 3DCRT. After a median follow-up of 21.9 months, 131 patients (26.2 %) developed HT and 59

(11.8 %) received thyroid replacement therapy. A $D_{mean} > 21$ Gy, again, was the threshold value for predicting HT after RT ($p < 0.001$). Another issue concerns secondary cancer risk as various reports have shown that even low doses may increase the risk of secondary thyroid malignancy development [108–110]. Based on this evidence, it is advisable to consider the thyroid gland as an OAR and accurately calculate the dose it receives and keep it as low as reasonably possible after fulfilling other, potentially more important dose constraints. In any case, regular monitoring of thyroid function through periodic serum assays is fundamental for prevention of clinically significant HT and, after early detection, appropriate treatment of manifest HT should be initiated. Thyroid dose constraints reported in the aforementioned studies are summarized in Table 4.

Chest wall toxicity and DVCs for chest wall

The CW includes both nerves and musculoskeletal tissue with an uncertain composite α/β value, for this reason the mechanism of CW toxicity is poorly understood [111]. Spontaneous rib fractures (SRFs) are defined as fractures without apparent blunt force trauma and are often asymptomatic. In patients treated for BC, SRF is linked to many causes. Known risk factors are represented by osteoporosis, RT, CT, use of AIs, and long-term use of bisphosphonates [112]. The effect of dose per fraction on the likelihood of radiation induced SRFs in BC patients remains controversial. As a starting point, after conventional fractionation Emami et al. estimated for SRFs, the 5 % and 50 % tolerance doses to be 50 and 65 Gy, respectively, to a third of the structure [72]. In a recent study the incidence of SRF, as identified by bone scans, was 16.5 % during follow-up [113]. Multivariate analysis of RT subgroups showed that hypofractionated RT increased the rate of SRFs ($p = 0.002$) [113].

To our knowledge, few detailed dose–response analyses have been conducted in association with SRFs after conventional fractionated or hypofractionated BC-RT.

Overgaard reviewed radiation-induced SRFs in 231 BCE patients who underwent postmastectomy RT; radiation-induced SRFs occurred in 19 % and 6 % of the large and standard fraction size groups, respectively (3.0–3.9 vs. 2.2–2.5 Gy/fraction); the difference was statistically significant and despite the technical limitations of 3-dimensional treatment planning are comparable to Emami's historic and rather unsystematic observations [114]. However, the 10-year follow-up data of the START trials [115] comparing conventional fractionation and hypofractionated RT of BC revealed no significant difference in the incidence of symptomatic rib fracture according to dose per fraction (1.5 % conventional vs. 2.2 % hypofractionation). A recent retrospective study analyzed the most relevant risk factors for ipsilateral SRFs in 2204 patients followed up with bone scans [116]. Ipsilateral SRF occurred in 14.5 % of patients 3 years after RT. Most of the patients with SRF (87.3 %) were asymptomatic. RT was administered according to two dose fractionation schemes: conventional fractionation and hypofractionated schedules. The number of patients who received each schedule is not specified and the authors used the same constraint for both schedules. Patients were treated with 3DCRT. In multivariate analysis $D_{2cc} \geq 52$ Gy EQD2 was the only significant risk factor for ipsilateral SRF and, viewing all available data synoptically, this seems to be the most reliable estimate of a clinically useful dose cutoff to date **in normo and hypofractionated RT**. CW dose constraints reported in the aforementioned studies are summarized in Table 4.

Spinal cord toxicity and DVCs for spinal cord

A very rare complication of BC-RT, particularly for patients undergoing RT of SCLNs, that should not have to be a real risk anymore today with the general availability of improved patient positioning, Image Guided Radiotherapy (IGRT) and IMRT and well understood dose-volume effects, has been post-actinic transverse myelitis. It is the result of damage to the white matter of the spinal cord (oligodendrocytes) and vascular damage to the endothelium (more frequently at low doses) [117]. The probability of actinic myelopathy is lower than 0.5 % with conventional fractionation for doses of 45–50 Gy. This side effect has a latency of months from the end of treatment, and it is more frequent in case of re-irradiation [118].

Based on literature data, there is no clear consensus on contouring modalities (only spinal cord, spinal cord + 2–3 mm, spinal canal) as these parameters depend, of course, on institutional patient positioning and treatment planning protocols, as well as on the upper and lower contouring limits. RTOG recommends 10 cm above and below the PTV as the limit for cord contouring to obtain reproducible and clinically meaningful dose-volume histograms (DVHs) [119].

As spinal cord at least longitudinally must be considered a serial OAR, attention must be, of course, paid to the administered maximum dose.

The following dose constraints may be recommended for left/right breast/CW plus SCLN treatments based on well established tolerance data derived from non-human primate studies as well as from long term follow up in patients treated for other diseases:

– **Conventional fractionation**: Dmax ≤ 45 Gy (optimal); Dmax 45–50 Gy (mandatory) [120].

– **Hypofractionation**: $D_{max} \leq 37.8$ Gy (optimal); D_{max} 37.8 Gy-42 Gy (mandatory) [121].

Given that treatment of metastatic vertebral disease may be necessary in the region of previous nodal treatment, spinal cord dose should ideally be limited to doses that permit an efficacious vertebral treatment after appropriate recovery (>6–12 months). Combining IGRT and IMRT/VMAT, cord doses can today reliably be limited to < 30 Gy, which also reduces spinal cord toxicity risk as a consequence of the first BC treatment effectively to zero [122].

DVCs for partial breast irradiation (PBI)

WBI has been conventionally delivered over several consecutive weeks, limiting access to breast-conserving surgery for women with socioeconomic barriers [123].

In early stage disease, local recurrence after breast conserving surgery occurs especially in the area of the primary tumour [124,125]. Treating only the tumour bed, PBI has therefore been suggested as a potentially more convenient treatment option for patients with early-stage BC [126], an approach that prior to publication of the results of accelerated WBI trials was considered a safe way to accelerate treatments in addition to expose less tissue.

Numerous large multicentric phase 3 trials demonstrated non-inferior local control in patients at low risk of recurrence, especially using external beam RT [127–129].

Based on these studies, several international guidelines consider the use of PBI a possible treatment paradigm in selected patients with early-stage BC. PBI can be delivered using different techniques (intra-operative RT, brachytherapy, and external beam RT) with various fractionation schedules. However, the results in terms of late toxicity and cosmetic outcome have so far differed among the studies. In IMPORT LOW (40.05 Gy/15 daily fractions), similar adverse effects were reported in the PBI and WBI arms [129]. In the RAPID trial, IRMA trial and NSABP B-39/RTOG 0413, despite the use of the same RT schedule (38.5 Gy/10 twice daily fractions), the results in terms of late side effects differed among the studies [127,128,130]. In RAPID, an increase in late soft tissue toxicity and skin telangiectasia was observed in patients treated with accelerated PBI (APBI) [127]. Similar results regarding late subcutaneous tissue toxicity were observed in IRMA [130], but the results regarding late skin toxicity differ between RAPID and IRMA. In NSABP B-39/RTOG 0413 late toxicity was similar between the two arms, although a detailed report has not yet been published [128]. There are several potential explanations for these conflicting results in terms of late toxicity and cosmesis. Radiobiologic models suggest that a twice-daily treatment might not permit complete repair of normal tissue

damage. Among other causes, some dosimetric parameters may have contributed to these contrasting results. The volume of ipsilateral breast receiving a high RT dose may have been associated with increased soft tissue toxicity, as recently shown by Thomsen et al [131]. Hot spots on the CW may have increased the risk of SRFs. Currently, very few publications from the main PBI trials analyze the correlation between the dose received by an OAR and the occurrence of side effects. It is therefore very important to evaluate DVCs retrospectively in these studies and standardise the DVCs in any future prospective trial to be able to collect the data for various treatment schedules and analyze them to identify any parameters predictive of toxicity. Recently, ASTRO therefore published recommendations on appropriate dose-fractionation regimens, target volume delineation, and treatment planning parameters for delivery of PBI [132]. In Table 5 we report DVCs used in the main PBI trials that can serve as general DVC recommendations as toxicity in these trials (that is also reported in the table) is in general acceptably low.

Discussion

To our knowledge, this is the first review of the literature that analyzed all available evidence regarding DVCs for BC-RT in a comprehensive fashion, including all OARs and different fractionation schedules and trying to correlate proposed DVCs with clinical endpoints if available.

Recently, results from European and Latin American surveys on organ-sparing techniques and DVCs in BC-RT were published [135]. Lungs (ipsilateral and contralateral), whole heart and CB resulted in the most frequently contoured OARs, with IMRT/VMAT as the preferred modalities used in heart sparing strategies. On the other hand, only a small percentage of all responders reported DVCs used in clinical practice, underlining the uncertainty about this issue, and MHD represented

Table 5
OARs dose constraints for PBI.

	Homolateral breast	Contralateral breast	Homolateral Lung	Contralateral Lung	Heart	Thyroid	Rib	Skin	Reported toxicities (only if different between the 2 arms)
IRMA Trial [130]	$V_{19.25Gy} < 60$ %	$D_{max} \leq 1.155$ Gy	$V_{11.55Gy} < 15$ %		$V_{1.92\ Gy}$	$D_{max} <$ 1.925 Gy			G3-4 late soft tissue: 2.8 % PBI vs 1 % WBI
(38.5 Gy/10 twice daily fractions)	$V_{38.5Gy} < 35$ %				<5% (right sided) <40 % (left sided)				G3-G4 late bone toxicity: 1.1 % PBI vs 0 % WBI
RAPID Trial[127]	$V_{19.25Gy} < 50$ %	$D_{max} \leq 1.155$ Gy	$V_{3.85Gy} < 20$ %	$V_{1.925Gy} < 5$ %	Right sided: $V_{1.925Gy} < 5$ %	$D_{max} <$ 1.925 Gy			G ≥ 2 induration: 22.9 % PBI vs 4.6 % WBI
(38.5 Gy/10 twice daily fractions)	(up to 60 %) $V_{36.575Gy} < 25$ % (up to 35 %)		$V_{11.55Gy} < 10$ %		Left sided (excluding lower inner quadrant): $V_{3.85Gy} < 5$ % Left sided (lower inner quadrant): $V_{5.775Gy} < 5$ %				G ≥ 2 telangiectasi: 9.3 % PBI vs 3.7 % WBI G ≥ 2 breast pain: 4.8 % PBI vs 1.9 % WBI
NSABP B-39 [128] (External beam RT: 38.5 Gy/10 twice daily fractions Brachytherapy: 34 Gy/10 twice daily fractions) *Only for External beam RT	$V_{50\%}$<60 % $V_{100\%}$<35 %	$D_{max} \leq 1.155$ Gy*	$V_{11.5Gy} < 15$ % *	$V_{1.925\ Gy} < 5$ % *	$V_{1.925\ Gy}$* <5% (right sided) < 40 % (left sided)	$D_{max} <$ 1.925 Gy *			No detailed data published
Florence Trial [133] (30 Gy/5 daily fractions every other day)	$V_{15Gy} < 50$ %	$D_{max} < 1$ Gy	$V_{10Gy} < 20$ %	$V_{5Gy} < 10$ %	$V_{3Gy} < 10$ %				G ≥ 2 overall late toxicity: 0 % PBI vs 7 % WBI
DBCG PBI trial [131] (40 Gy/15 daily fractions)	$V_{40\%}$<50 %		$V_{17\%}$<25 %		$V_{35\%}$<5% $V_{17\%}$<10 % $D_{max(LADCA)} \leq$ 17 Gy				G ≥ 2 Breast induration: 5.1 % PBI vs 9.7 % WBI
IMPORT LOW [129] (40 Gy/15 daily fractions)	Not defined in the protocol								
ESTRO-ACROP	Ipsilateral non-target breast		MLD < 8 %		MHD < 8 %		$D^3_{0,1cm}$ < 90 %	D^3_{1cm} < 90 %	
Brachytherapy [134]	$V_{90\%}$<10 % $V_{50\%}$<40 %		$D^3_{0.1cm} < 60$ %		$D^3_{0.1cm} < 50$ %		D^3_{1cm} < 80 %	$D^3_{0.2cm}$ < 100 %	

MLD: Mean lung dose; MHD: Mean heart dose; PBI: Partial Breast Irradiation; WBI: Whole Breast Irradiation; D_{max}: Maximum dose. Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

the most frequently reported parameter.

The introduction in clinical practice of more advanced delivery techniques has prompted the necessity to adapt/redefine dose constraints in BC-RT.

A definitive proposal of DVCs for main OARs (such as lungs, heart and CB) is difficult to establish but should most likely prioritize the possibility to reduce the high doses despite a relative increase of mean and low doses.

Regarding lung DVCs, most clinical data correlated with specific dosimetric parameters derive from studies on RT in lung cancer. In the few published single centre studies focusing on RP incidence after breast RT 3DCRT (tangential fields) was the most frequently used technique. In the setting of conventional fractionation, MLD and V20Gy were considered as robust predictors of RP, as the incidence of RP rises significantly at V20Gy > 20–30 % of the ipsilateral lung volume and/or at MLD values > 10–15 Gy [11,14,22–27]. International guidelines and ongoing trials re-proposed these parameters for both conventional and hypofractionated regimens, without differences based on the employed technique. The use of IMRT should be able to reduce MLD_{ipsi} and V20Gy for more extensive targets such as in IMC irradiation, but it increases contralateral lung dose. As for doses to the CB, there remain some concerns about the larger volumes treated to low doses and a potential relationship with an increase of SC incidence, but only long term clinical follow up will be able to clarify this issue. Fogliata et al. tried to evaluate the impact of VMAT breast treatments when compared to 3DCRT on SC Excess Absolute Risk (EAR), taking into account Normal tissue complication probability (NTCP) to estimate the ipsilateral lung, heart, and skin toxicity [136]. With obvious limitations related to the type of study (in silico study), the authors concluded that VMAT (particularly the VMAT_tang setting) could have the same risk of SC induction as 3DCRT delivered with the Field-in-Field setting for the contralateral organs while reducing acute and late NTCP for the ipsilateral organs. It is not yet clear what DVC is most relevant to increase SC risk, especially because of several confounding factors such as a small number of events detected with difficulties in collecting long-term follow-up data and the unclear effects of other elements (chemo-endocrine therapy, genetic predisposition or smoking habit) [19,20]. In synthesis the use of modern RT techniques (IMRT/VMAT/Tomotherapy), particularly when more extensive targets have to be irradiated, allows to optimize the lung DVCs reducing toxicity, so far without evidence of an increase of SC risk.

Heart DVCs, in this context, merit a more in-depth discussion. Currently, based on data generated from 3DCRT-series MHD is the most commonly used constraint in clinical practice as several studies showed that a reduction of MHD is associated with lower risks of cardiac late effects. However, as demonstrated by other previously cited studies, the use of MHD alone has limitations.

Piroth et al. showed that using a simple wedged tangential field technique, a low MHD is achievable (mean 2.1 Gy [SD 1.32]) but, despite such a low MHD, small but relevant subvolumes such as the heart apex or parts of the LAD can be exposed to much higher doses (mean LAD Dmax: 24.6 [SD 17.6]) [137]. Similar results were reported by Tan et al. evaluating dose distributions achievable with IMRT [59]. They also concluded that the “anterior myocardial territory” may replace the heart as the OAR in left-sided breast IMRT to decrease the radiation dose to the heart. Therefore, even when relying only on (modified) tangential techniques, as a consequence of individual patient anatomy, MHD may often remain below 2.5/3Gy but apical areas like LAD and LV receive much higher doses. To limit high doses to these substructures, it is crucial to use additional dose limits (as reported in Table 2) in addition to MHD and, when required, adequate techniques as comprehensively reported and recommended by the DEGRO review on heart-sparing RT techniques in BC patients [138].

A limitation of the reviewed datasets and, as a consequence, of this review, is the absence of specified contouring guidelines for a large number of the discussed OARs. This aspect may, of course, represent a source of uncertainty for the entire analysis and for this compilation of suggested DVCs as the amount of the variation in contouring across the manuscripts this review is based on are unknown. Given the fact that more recently the number of available contouring guidelines has increased and contouring in study populations is usually well controlled, contouring variation is, however, likely smaller than in the past.

On the other hand, the main strength of this work is to provide a comprehensive summary of DVCs for BC-RT that may help to harmonize treatment planning strategies, based on available data, which in turn would lead to an increase of the reliability/robustness of dose/response-effect relationship estimates as the analysis of these future, more aligned prospective efforts would likely be more reliable and accurate, improving the quality of real-world clinical data with large numbers. Moreover, the addition of some very restrictive but achievable DVCs, as suggested above for the heart, could accelerate the adoption of heart-sparing RT techniques, as well as PBI when indicated, in clinical practice.

Since modern and more conformal techniques are now widely available for WBI and RNI, patient anatomy and treatment volumes must guide the choice of technique in order to obtain the best possible treatment plan for all patients taking into account target coverage, dose homogeneity and refined OAR sparing.

Conclusions

This review provides clinically useful information regarding DVCs to avoid radiation-induced toxicity in BC-RT in the most comprehensive detailed fashion that is currently achievable across all commonly used treatment paradigms. While ongoing studies and incoming long-term data will further refine these data, this review may serve as a practical summary of the currently available literature data.

CRediT authorship contribution statement

Fiorenza De Rose: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization. **Maria Carmen De Santis:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization. **Sara Lucidi:** Writing – review & editing, Writing – original draft. **Riccardo Ray Colciago:** Writing – review & editing, Writing – original draft. **Lorenza Marino:** Writing – review & editing, Writing – original draft. **Francesca Cucciarelli:** Writing – review & editing, Writing – original draft. **Eliana La Rocca:** Writing – review & editing, Writing – original draft. **Francesca Di Pressa:** Writing – review & editing, Writing – original draft. **Frank Lohr:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Valentina Vanoni:** Writing – review & editing, Writing – original draft. **Bruno Meduri:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization.

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