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Organ-sparing techniques and dose-volume constrains used in breast cancer radiation therapy – Results from European and Latin American surveys

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ABSTRACT

Background: Advances in local and systemic therapies have improved the outcomes of patients with breast cancer (BC), leading to a possible increased risk for postoperative radiation therapy (RT) late adverse events. The most adequate technologies and dose constraints for organs at risk (OAR) in BC RT have yet to be defined.
Methods: An online survey was distributed to radiation oncologists (ROs) practicing in Europe and Latin America including the Caribbean (LAC) through personal contacts, RO and BC professional groups' networks. Demographic data and clinical practice information were collected.
Results: The study included 585 responses from ROs practicing in 57 different countries. The most frequently contoured OAR by European and LAC participants were the whole heart (96.6 % and 97.7 %), the ipsilateral (84.3 % and 90.8 %), and contralateral lung (71.3 % and 77.4 %), whole lung (69.8 % and 72.9 %), and the contralateral breast (66.4 % and. 83.2 %). ESTRO guidelines were preferred in Europe (33.3 %) and the RTOG contouring guideline was the most popular in LAC (62.2 %), while some participants used both recommendations (13.2 % and 19.2 %). IMRT (68.6 % and 59.1 %) and VMAT (65.6 % and 60.2 %) were the preferred modalities used in heart sparing strategies, followed by deep inspiration breath-hold (DIBH) (54.8 % and 37.4 %) and partial breast irradiation (PBI) (41.6 % and 24.6 %). Only a small percentage of all ROs reported the dose-volume constraints for OAR used in routine clinical practice. A mean heart dose (Heart-D_{mean}) between 4 and 5 Gy was the most frequently reported parameter (17.2 % and 39.3 %).
Conclusion: The delineation approaches and sparing techniques for OAR in BC RT vary between ROs worldwide. The low response rate to the dose constraints subset of queries reflects the uncertainty surrounding this topic and supports the need for detailed consensus recommendations in the clinical practice.

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1. Introduction

Radiation therapy (RT) is an integral part of breast cancer (BC) multidisciplinary treatment, reducing the risk of both recurrence and BC mortality [1,2]. Improvements in BC treatment increase patients' survival and hence lead to an increased concern for late toxicities.

The risk of cardiac damage persists for decades after radiation exposure and the "safe dose" threshold is not firmly established [3–7]. Based on older studies, the risk of ischemic heart disease or sudden cardiac death rises proportionally by 6.4–16.5 % for every Gy of radiation absorbed by the whole heart [3,8,9]. Especially when treating patients with left-sided BC, minimizing the dose to the heart can be challenging. In sharp contrast, a recent *meta*-analysis of lymph node irradiation showed that, in the 12.167 patients who were treated in the 8 trials starting after 1989, no significant effect on non-breast-cancer mortality (RR = 0.97, p = 0.63) was seen, leading to an overall clinically relevant survival benefit in favour of nodal RT [10].

Focused analysis on cardiac substructures showed differences in toxicity. The dose received by left anterior descending coronary artery (LAD) and the volume of the left ventricle (LV) receiving 5 Gy (V5) were found to be better predictors for adverse cardiac events than Heart Dmean [8,11]. Moreover, systemic therapies can have a detrimental cumulative effect [12].

Although the lung radiation exposure is relatively low during breast or chest wall RT, subsequent secondary tumours or lung fibrosis are potential risks, namely in smokers [9,13]. Radiation volume, patient positioning, and RT delivery technique influence the dose received by organs at risk (OAR) [14].

Intensity Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) or Deep Inspiration Breath Hold (DIBH) improved conformity and/or reduced the risk of delivering high dose to the heart and the lungs [15], decreasing both acute and late toxicities [14,16–21]. In patients treated with partial breast irradiation (PBI) the Heart-D_{mean} was four times lower and the Lung-D_{mean} was twice lower compared to IMRT [22]. Reducing the high doses to the heart and lungs with IMRT or VMAT techniques comes with the cost of a low-dose irradiation of these volumes and the contralateral breast, increasing the risk of a radiation-induced secondary cancer [23,24].

At present, there are detailed contouring guidelines [25–27], but no practical recommendations for doses to OAR, except for the heart, from the German Society for Radiation Oncology group (DEGRO) [16].

With this survey, we aimed at providing real-world data regarding the current BC clinical practice with respect to BC RT techniques and sparing of the OAR.

2. Material and methods

From October 2019 to March 2020, a web-based quantitative questionnaire was distributed to practicing ROs in Europe via personal contacts, national and international radiation oncology society networks. The same 38-question questionnaire was used in an online survey undertaken by the practicing ROs in the Latin America and the Caribbean (LAC) between February and March 2022. Collected data were completely anonymous. For this type of study, ethical approval was not needed. The survey was developed using the 1KA survey platform in Europe and REDCAP platform in LAC and covered a variety of RT practice topics for patients with BC. The details and the questionnaire used in the study have been previously described [29,30]. The questions were designed on a multiple-choice framework, allowing for multiple and free-text responses. The results reported in this paper focus on the use of organ-sparing techniques and dose constraints for BC RT. If not otherwise specified, the values in the text represent relative percentages, calculated from responses having at least one option chosen for a certain question. Absolute percentages, calculated relative to the total number of participants, are mentioned in the supplemental tables. For the questions with an answering rate below 50 only absolute percentages were provided. Included in the statistical analyses were descriptive statistics, chi-square and Kruskal-Wallis tests. All analyses were two-sided, and p values 0.05 were considered statistically significant. Statistical analyses were carried out using IBM SPSS Statistics software version 26 (statistical package for the Social Sciences Statistical Software; SPSS Inc., IBM corporation, Armonk, NY, USA). Figures were created using Microsoft® Excel® for Office 365 version 1812 (Microsoft Corporation, One Microsoft Way Redmond, WA, USA).

3. Results

Five hundred and eighty-five ROs (412 from Europe and 173 from LAC) from 57 countries (45 Europe, 13 LAC) participated in the survey. More than half of those who responded worked in public and/or university hospital settings, had at least ten years of experience, and treated more than ten patients with BC per month (Supplemental Table 1).

In clinical practice, most European and LAC participants contoured the entire heart (96.6 % and 97.7 %), ipsilateral lung (84.3 % and 90.8 %), the contralateral lung (71.13 % and 77.5 %), and the whole lung (69.8 % and 72.8 %), respectively ROs from LAC were more likely to delineate the contralateral breast (66/4% and 83.2 %) than ROs from European countries. Cardiac substructures such as the left anterior descending coronary artery (LAD) (30.6 % and 28.3 %) and the LV (11.7 % and 13.9 %) were less likely to be contoured by either European or LAC respondents compared to the whole heart, lungs or contralateral breast (Fig. 1).

One third of the European ROs mentioned European SocieTy for Radiotherapy and Oncology (ESTRO) guidelines as the main reference for contouring volumes for BC radiation therapy. The ESTRO category included ESTRO 2015 and/or ESTRO-Advisory Committee for Radiation Oncology Practice (ACROP) 2019. Twenty-nine of the European ROs% preferred to use RTOG only, and 13.2 % declared to use a combination of both ESTRO and RTOG. More ROs from Europe used other guidelines, like institutional ones, or a combination of ESTRO, RTOG and other recommendations. In the LAC, RTOG was preferred by 62.2 % of respondents, while other 19.2 % were using both RTOG and ESTRO (Fig. 2).

Most participants had access to heart-sparing modalities such as IMRT and VMAT, followed by DIBH and PBI. Proton therapy was rarely available in clinical practice and very few participants used more than one heart sparing technique for the same patient (Fig. 3).

DIBH and/or gating techniques were preferred in the workplace of 54.8 % of the European participants and 37.4 % of the LAC participants, and it was used for selected patients. When treating the left breast, 27 % of European and 12.9 % of Latin American ROs employed this approach for more than three quarters of the patients. For the right BC, most of the respondents used DIBH for less than a quarter of the patients or not at all (Fig. 4). The main reason for choosing DIBH for the right BC was the sparing of heart (55.2 % and 39.3 %) or lung (60.4 % and 34.5 %). The lack of appropriate equipment was the primary reason for not utilizing this technique (35.5 % and 43.9 %), followed by the lack of trained human resources (20.3 % and 24.3 %) and the increased treatment time required when implementing this technique (30.4 % and 20.8 %) in Europe in LAC, respectively (Supplemental Table 4).

PBI was mentioned as part of the clinical practice by 61.4 % of the responding European and 50.6 % of LAC ROs, respectively (Supplemental Table 5). When answering more detailed questions on this topic, most respondents declared they used it in selected cases or for patients enrolled in clinical studies. The most widely used technique for PBI was external beam IMRT/VMAT followed by mini tangents or 3D-CRT (28.9 %) and interstitial brachytherapy (Fig. 5).

The lowest response rate was observed for questions regarding dose-volume constraints, with a maximum of 33.3 % and 49.1 %. Regarding Heart-D_{mean}, the majority of responding ROs reported using values between 4 and 5 Gy (17.2 % and 39.3 %), whereas only a minority reported using values below 3 Gy. Only 6.8 % of the ROs from Europe and 14.4 %

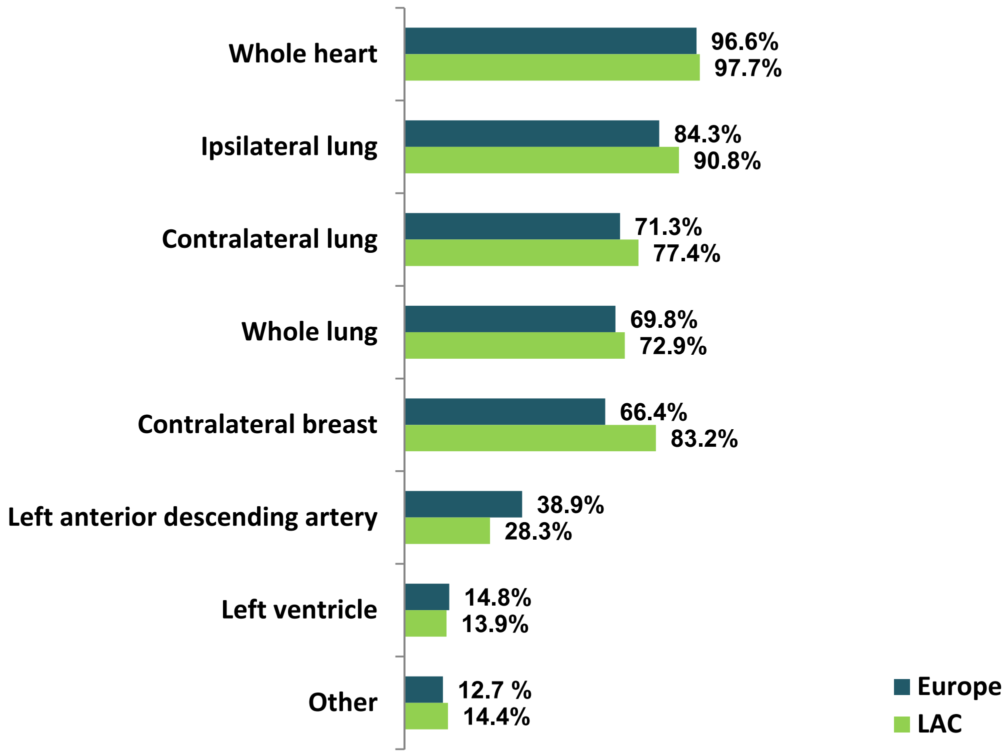

Fig. 1. Structures routinely delineated for postoperative breast cancer radiation therapy. The bar charts in the figure represent percentages from valid answers. Abbreviations: LAC = Latin America and the Caribbean.

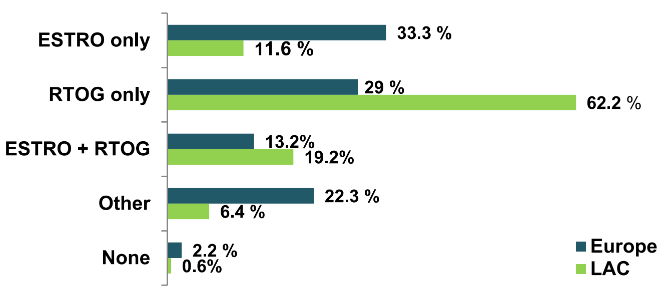

Fig. 2. The favourite guideline for target volume delineation in case of postoperative radiation therapy for early-stage breast cancer. The bar charts in the figure represent percentages from valid answers. Abbreviations: RTOG = Radiation Therapy Oncology Group, ESTRO = European SocieTy for Radiotherapy and Oncology, LAC = Latin America and the Caribbean.

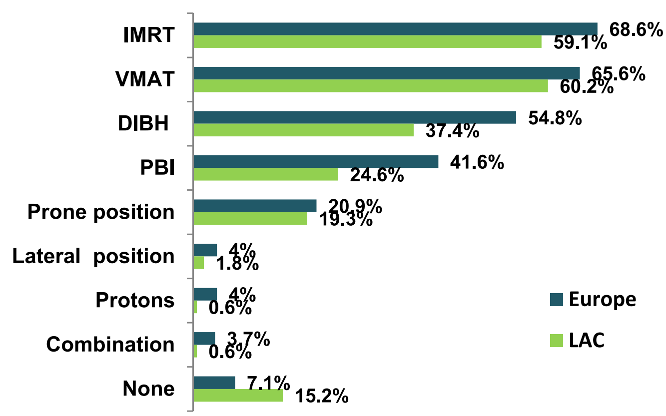

Fig. 3. Heart sparing techniques used in participants' place of work. The bar charts in the figure represent percentages from valid answers. Abbreviations: IMRT = Intensity Modulated Radiation Therapy, VMAT = Volumetric Modulated Arc Therapy, DIBH = Deep Inspiration Breath Hold, PBI = partial breast irradiation, RT = Radiation Therapy, LAC = Latin America and the Caribbean.

from LAC reported values of dose constraints for cardiac substructures; however, the mentioned values varied relevantly in clinical practice. For instance, the reported LAD-D_{max} varied from 10 to 40 Gy among European participants and from 3 to 19 Gy for LAC. Likewise, only a small percentage of all responding ROs reported dose-volume constraints to evaluate dose to the lung i.e., Lung-D_{mean} values (8 % and 16.2 %) or the ipsilateral lung V20 (17.2 % and 30.6 %) (Supplemental Table 6).

For European data, significant correlation was found between the reported Heart-D_{mean} used in routine clinical practice and the percentage of the time dedicated to BC RT treatments ($p = 0.025$) and the multidisciplinary decision making for adjuvant postoperative RT ($p = 0.006$). According to the heart sparing technique a significant correlation of the reported Heart-D_{mean} (lower dose constraint used in clinical practice) was found with those ROs who use DIBH ($p < 0.002$). None of the factors had an impact in the reported ipsilateral lung-D_{mean}. For LAC data, None of the factors had an impact in the reported ipsilateral heart-D_{mean} or lung-D_{mean}.

4. Discussion

Our study is a joint overview of OAR sparing approaches in BC RT in European and LAC countries, with an emphasis on heart and lung sparing techniques used in clinical practice and on corresponding dose-volume constraints. According to the results of our survey, the OAR delineation and sparing techniques in BC RT varies considerably. The whole heart was the most frequently OAR delineated by the participants, approximately one third also contoured the LAD, and less than a tenth contoured the LV. The ipsilateral lung was routinely delineated by 9 of 10 and the whole lung was contoured by 7 from 10 respondents, respectively. The participating ROs were asked to report the dose-volume restrictions they employ most frequently in clinical practice,

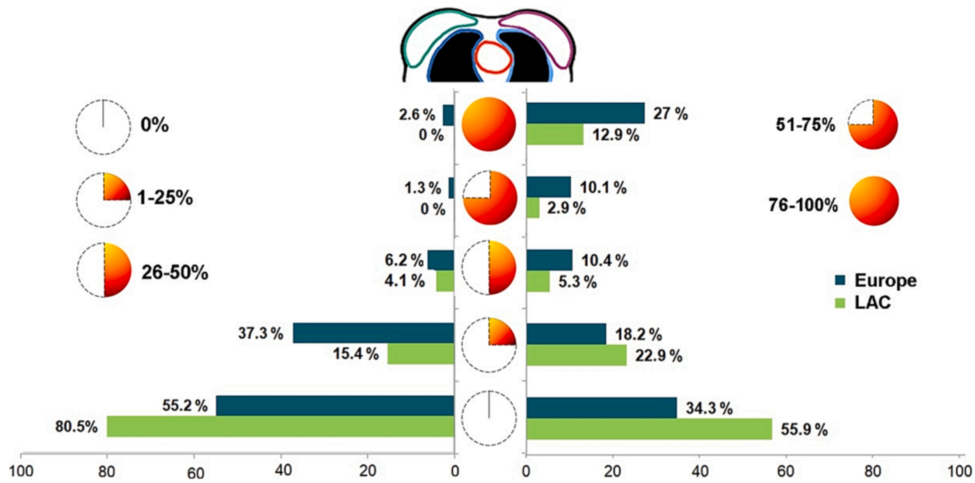

Fig. 4. Details on the use of deep inspiration breath hold and/or gating techniques. The bar charts in the figure represent percentages from valid answers. The percentages on the right represent preferences for left BC patients, and the percentages on the left, for right BC patients, respectively. Pie diagrams represent the approximate proportion of BC patients for either left or right BC, for which DIBH is routinely used. LAC = Latin America and the Caribbean.

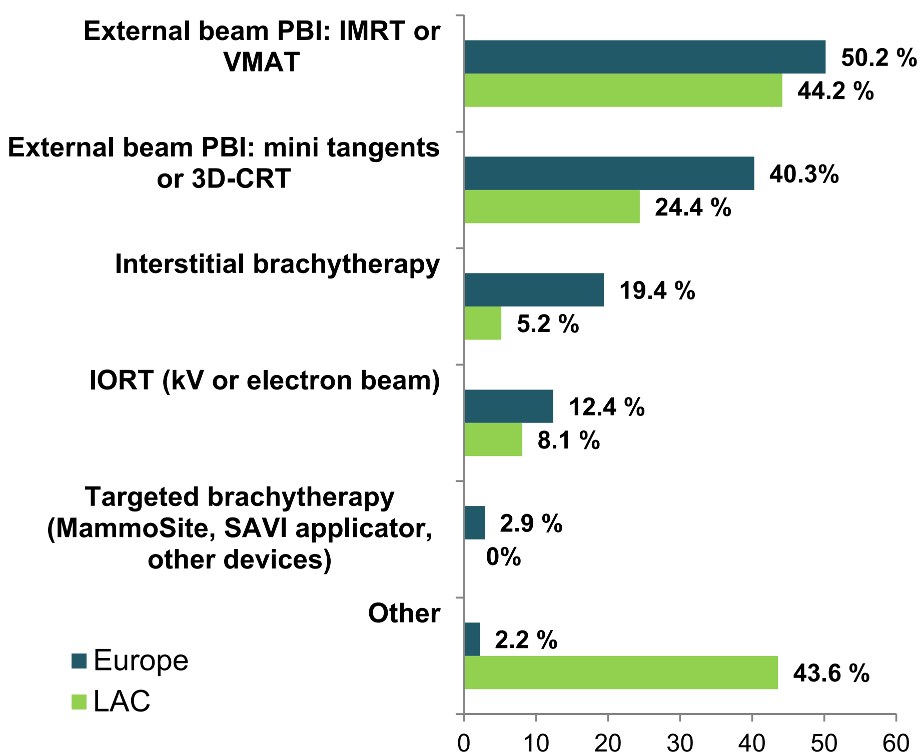

Fig. 5. Details techniques used for partial breast irradiation. Abbreviations: IMRT = Intensity Modulated Radiation Therapy, VMAT = Volumetric Modulated Arc Therapy, DIBH = Deep Inspiration Breath Hold, PBI = partial breast irradiation, RT = Radiation Therapy, 3D-CRT = 3D conformal radiation therapy, IORT = Intra-operative RT, kV = kilovoltage,), LAC = Latin America and the Caribbean.

but the response rate was extremely low.

In comparison to the RTOG, the ESTRO guidelines use smaller, anatomy-based, clinical target volumes [31]. According to our findings, the RTOG contouring guidelines are used by the vast majority of ROs from LAC and surprisingly, it seems to be the preferred option among almost one third of European ROs, too. In Europe, the ESTRO guidelines are preferred by only one third of the respondents and used together with RTOG by another 13 %. By contrary, the ESTRO guidelines are more popular in Australia and New Zealand, according to the survey evaluating patterns of practice for BC RT in these countries. In that survey, only 67.6 % of ROs reported delineating target volumes, while 32.4 % reported employing conventional field-based techniques. Those who did not outline the target volumes, however, stated that they would begin doing so when employing more conformal techniques [32].

IMRT and VMAT are the most frequent implemented heart sparing solution in both European and LAC countries, according to our results. They were equally popular, being chosen by 60–70 % of the respondents. A slightly lower percentage was reported in South Korea (52 %) [33]. A DEGRO survey evaluating patterns of practice from Germany, Austria and Switzerland reported a lower popularity of these techniques as organ-sparing modalities and a preference for IMRT compared to VMAT (22.1 % and 5.9 %) [34]. However, these percentages are not equivalent with those reported by our study, since the German results reflect the proportion of departments using a certain technique as preferred option, and our question allowed multiple answers mentioning all the implemented techniques in the department where the participant was working. Data regarding the superiority of one technique or the other is heterogeneous and he results can be dependent on patient's anatomy, study sample size and planning optimization [35,36]. However, most of the results show that both inverse-planning methods significantly decrease OAR' D_{mean} and high-dose volumes but not the low-dose volumes [19,37–39].

According to the results of our survey, a respiratory control technique such as DIBH was selected as preferred organ-sparing technique by 54.8 % and 37.4 % of the participants. While answering a more detailed question, 37.1 % of European and 15.8 % of Latin American ROs acknowledged using respiratory techniques for more than half of the patients with left BC. In the DEGRO survey, the breathing adapted RT was the preferred heart-sparing technique being mentioned by 65 % of the participants. In the USA also, it was the most implemented technique for this purpose. Forty three percent of the respondents declared using DIBH more than three-fourths of the time, approximately with the same frequency for whole-breast or chest wall irradiation alone or with regional nodal irradiation, for patients with left BC [40]. In the Australian survey, the availability was similar with our results (44.2 %), but more than half of the ROs who had it in their department, employed it for all the patients with left-sided BC [32]. In our study, this proportion was lower, as only 27 % of European and 12.9 % of LAC ROs were implementing it for more than three thirds of this category of patients. In a survey from South Korea, only 14 % of the ROs were using this technique [33]. The main reasons for not using DIBH by the participants in our survey was the lack of proper equipment or trained human resources, followed by logistic challenges, like additional time slots needed. In the USA, 61 % of those who were not using it mentioned the lack of facilities as main reason [40].

Except for using more precise technology in order to decrease the heart dose, there are additional tools to decrease the cardiac toxicity risk. Cardiovascular disease risk factors like diabetes and smoking modify the risk profile of the patient. When comparing the risk decrease from ceasing smoking to the one provided by using DIBH instead of free breathing, the behaviour change seems to be even more beneficial [41]. The DEGRO BC expert panel recommends DIBH as the best heart-sparing technique and its combination with IMRT for treating the internal mammary lymph node areas [15]. Treatment using DIBH in the supine position is correlated with a lower Heart-D_{mean} and therefore less cardiac toxicity [8,42–44]. A recent ESTRO guideline provides an overview of available technical solutions and guidance for best practice in the implementation phase of the DIBH. As breath-hold techniques can contribute to a more targeted treatment delivery and/or permit greater sparing of adjacent OAR, each institution should determine the most effective and suitable DIBH strategy according to their available resources [45].

Approximately one third of all responding ROs chose PBI as one of the preferred heart-sparing technique, acknowledging its use for selected patients. In the Korean survey, the use of PBI was only 4.7 % [33]. In Germany, a significant difference was found between the use of PBI in the university hospitals compared to other departments (25 % and 3 %, respectively) [34]. PBI is superior to whole breast irradiation in terms of cardiac dose reduction. However, the dose reduction is comparable between DIBH and PBI with multi catheter brachytherapy [16].

The prone position technique was chosen as a treatment option by only 17 % of responding ROs in Europe and 19 % in LAC countries. In Korea, the percentage of ROs using the prone position for cardiac preservation was less than 10 % [33], while the proportion in the Australian survey was twice that of Europe [32]. By minimizing chest wall and respiration-related surgical clip motions, the prone position has shown dosimetric advantages over the supine position [46]. Additionally, the prone position can decrease heart, LAD, and ipsilateral lung irradiation during postoperative RT for BC without affecting mean dose of target coverage [47]. Additionally, when women with large breast size receive postoperative RT, therapy in the prone position reduces skin desquamation [48]. However, the prone position might be associated with worse setup accuracy [49].

In our survey, the questions regarding the dose constraints had the lowest response rate and the answers were heterogeneous (Supplemental Table 6). These results might reflect a degree of uncertainty on thresholds, an insufficient standardisation, or a lower priority of some parameters for planning approval. The most frequently mentioned parameter was the Heart-D_{mean}, the preferred option being 4–5 Gy. Current trials are using a Heart-D_{mean} of 3–5 Gy as acceptable for BC RT treatment panning [50]. New data on the clinical impact of a certain dose received by cardiac substructures supports the need for detailed contouring. Dosimetric evaluation of the Heart-D_{mean} and doses received by cardiac substructures showed that this parameter is not relevant for predicting the dose received by the LV and coronary arteries. More than half of the patients with left sided BC with Heart-$D_{mean} < 3$ Gy could receive doses above 40 Gy to the LAD [51]. Although studies have found a link between RT exposure to the coronary arteries and coronary artery stenosis [52] and clinical data suggest that the volume of the LV receiving 5 Gy (V5) may be a better predictor of adverse cardiac events than Heart-D_{mean} [9], cardiac substructures are not routinely delineated in clinical practice.

In a recently published prospective longitudinal cohort, pulmonary medical history (OR = 3.05, $p = 0.01$) and higher V30 Gy (OR = 1.06, $p = 0.04$) remained statistically significant risk factors for radiation-induced lung injury (RILI) incidence. In a multivariable analysis, V30 Gy > 15 % was significantly associated with the occurrence of RILI (OR = 3.07, $p = 0.03$) [53].

Table 1 and 2 summarize dose-volume constraints from clinical trials, professional group recommendations, and systematic reviews for heart and lung, respectively.

Updated and detailed recommendations for patient selection for certain techniques and adequate dose-volume constraints, like the recently published ASTRO Clinical Practice Guideline for PBI are welcomed to improve standardisation [57].

To our knowledge, this is the first study evaluating details on OAR delineation, dose constraints and sparing techniques for BC RT in Europe and LAC countries. However, there are some limitations which need to be taken into account. The participants' number and answers might not be representative for the ROs' from each country and situation might have slightly changed from the moment the data was collected. The questions did not include an option for multisegment techniques ("forward-IMRT"), so the respondents might have assimilated it either in the 3D-CRT or IMRT options. Due to inherent variations in patients' anatomy or clinical situations, as well as possible challenges of complex planning, the use of a certain technology cannot be considered as a quality indicator surrogate. The number of the answers acknowledging the availability of DIBH and PBI was slightly lower than the sum of the answers giving details about indication and treatment details of those techniques. This might be explained if some participants expressed the preference for a certain OAR sparing technique when more options were available. Alternatively, some could have expressed their theoretical preference instead of the clinical practice in their workplace. When the answers reflected that a certain technique was not used, we could not differentiate if the reasons were subjective (preference) or objective (availability). The low answering rate for dose-volume constraints decrease the representativeness of the data, but we consider that the avoidance of answering those questions has an important significance in itself. Another limitation of the results is caused by the difficulty to provide enough details to discriminate the different dose constraints used in the clinical practice for different techniques, irradiation schedules or other particular situations (dose fractionation, including boost addition, or boost anatomical location).

Table 1
Dose-volume constraints for heart and cardiac substructures.

Parameter	Value	Comments	Source
Heart D_{mean}	3.3 Gy	Right breast	Taylor [54]
	3.5 Gy	Whole breast	Taylor [54]
	4.2 Gy	Left breast plus IMC	Taylor [54]
	5.4 Gy	Left breast	Taylor [54]
	0.5–14.3	IMRT	Taylor [54]
	<26–30 Gy		Bisello [55]
	<1–2 Gy	Left breast alone	Smith [44]
	<1 Gy	Right breast alone	Smith [44]
	<2.5 Gy	Breast without regional node irradiation	Piroth [28]
	<2.5 Gy	APBI	Strnad [56]
	<1.5 Gy	Left breast PBI EBRT HF/ultra-HF	Shaitelman [57]
	<0.8–1.6 Gy RBE	Left breast proton therapy	Fagundes [58]
	<1 Gy RBE	Left breast plus IMC with proton therapy	MacDonald [59]
	<1.0 (0.09–3.20)	Left breast proton therapy	Cuaron [60]
	<0.7 Gy	Right breast PBI EBRT HF/ultra-HF	Shaitelman [57]
	<0.5 Gy (RBE)	Left breast locoregional proton therapy	Mutter [64]
Heart D 0.1 cm^3	<50 %	APBI	Strnad [56]
Heart V3	≤10 %	APBI	Marrazzo [61]
Heart V5	≤5%	Right breast PBI EBRT HF/ultra-HF	Shaitelman [57]
Heart V7	<5%	Ultra-HF	Sigaudi [63]
Heart V1.5	<30 %	Ultra-HF	Sigaudi [63]
Heart V15	≤5%	Left breast PBI EBRT HF/ultra-HF	Shaitelman [57]
Heart V17	<10 %	HF – loco-regional	Thomsen [64]
Heart V17	<5%	HF – whole breast	Thomsen [64]
Heart V20	<10 %	CF	Thomsen [64]
Heart V20	<1.16 (0–6.0) Gy (RBE)	Left breast proton therapy	Cuaron [59]
Heart V25	<10 %	CF	Bisello; Bentzen [55,65]
Heart V30	<30 %	CF	Bisello [55]
Heart V35	<5%	HF – loco-regional	Thomsen [64]
Heart V35	<1%	HF – whole breast	Thomsen [64]
Heart V40	<5%	CF	Thomsen [64]
Pericardum D_{mean}	<26 Gy	<15 % pericarditis	Bentzen [65]
Pericardum V30	46 %	<15 % pericarditis	Bentzen [65]
LV D_{mean}	<3 Gy		Piroth [28]
LV V5	<17 %		Piroth [28]
LV V23	<5%		Piroth [28]
LAD D_{mean}	<10 Gy		Piroth [28]
LAD D_{max}	20 Gy	CF	Thomsen [64]
LAD D_{max}	17 Gy	HF	Thomsen [64]
LAD D_{max}	4.7 Gy (RBE)	Proton therapy	Mutter [60]
LAD V15	<10 %		Bisello [55]
LAD V30	<2%		Piroth [28]
LAD V40	<1%		Piroth [28]

Abbreviations: IMRT = Intensity Modulated Radiation Therapy; APBI = Accelerated Partial Breast Irradiation; PBI = Partial Breast Irradiation; IMC = Intra Mammary Chain; HF = Hypo fractionation; ultra-HF = Ultra-hypofractionation; CF = Conventional Fractionation; LV = Left Ventricle; LAD = Left Anterior Descending coronary artery; Vx = percent volume of the organ receiving x Gy radiation; Dx = dose received by organ at a defined volume (x) in percentage; D_{min} = minimal absorbed dose; D_{max} = maximal absorbed dose; D_{mean} = mean absorbed dose; RBE = relative biologic effectiveness.

Table 2
Dose-volume constraints for lung.

Parameter	Value	Comments	Source
Lung-D_{mean}	<3–4 Gy <1–1.5 Gy for stochastic effects	APBI	Strnad [56]
Lung-D_{mean}	≤20–23 Gy	Whole lung; CF; to limit the risk of RP to ≤ 20 %	Marks [64]
Lung D 0.1 cm^3	<60 %	APBI	Strnad [56]
Ipsilateral lung V10	≤20 %	APBI	Marrazzo [61]
Ipsilateral lung V8	<15 %	Ultra-HF	Sigaudi [63]
Ipsilateral lung V20	<15 % (ideal) <20 % (acceptable)	CF	Smith [44]
Ipsilateral lung V16	<15 % (ideal) <20 % (acceptable)	HF	Smith [44]
Ipsilateral lung V20	<25 %	CF	Thomsen [64]
Ipsilateral lung V20	<17 %	HF	Thomsen [64]
Ipsilateral lung V20 (RBE)	<15 %	Proton therapy	MacDonald [59]
Ipsilateral lung V20 (RBE)	<16.50 (6.1–30.3)	Proton therapy	Cuaron [60]
Ipsilateral lung V20 (RBE)	<14.5 %	Proton therapy	Mutter [62]
Ipsilateral lung V30	≤10 %	Left breast PBI EBRT HF/ultra-HF	Shaitelman [57]
Lung V20	≤30–35 %	Whole lung; CF; to limit the risk of RP to ≤ 20 %	Marks [66]
Contralateral lung V5	≤10 %	APBI	Marrazzo [61]
Contralateral lung V10	≤5%	Left breast PBI EBRT HF/ultra-HF	Shaitelman [57]

Abbreviations:C F = Conventional Fractionation; HF = Hypofractionation; Vx = percent volume of the organ receiving x Gy radiation; Dx = dose received by organ at a defined volume (x) in percentage; D_{mean} = mean absorbed dose; RBE = relative biologic effectiveness; PBI = Partial Breast Irradiation; ultra-HF = ultra-hypofractionation: EBRT = External Bean Radiation Therapy.

5. Conclusion

OAR delineation for BC RT has a high variability in clinical practice. IMRT/VMAT are the preferred modalities for organ sparing, while availability of DIBH and implementation of PBI is increasing. Heart-D_{mean} is the most frequently used parameter for evaluating treatment planning and experienced radiation oncologists typically use a lower threshold. Overall, dose-volume constraints questions had a low answering rate, reflecting uncertainty. Evidence—based recommendations and general consensus on OAR dose for various RT techniques and treatment schedules could increase consistency in BC RT and thereby improve treatment quality, decreasing the risks for adverse events.

Statements

Author's contribution: Conceptualization and Methodology: IR, MEC; Investigation: IR, MEC, GNM; Data curation: IR, FK, GNM, WFPNJ, GAV, AGG; Formal analysis: IR, FK, GNM, WFPNJ; Project administration: IR; MEC, GNM, Resources: IR, MEC, GNM, Software: IR; GNM; Supervision: IR; Validation: IR; GNM, Writing – original draft: FK, MEC, IR; Writing – review & editing: IR, MEC, FK, PF, PP, GNM, GAV, AGG, WFPNJ.

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Monica-Emilia Chirila: Conceptualization, Methodology, Data curation, Writing – original draft, Project administration, Resources, Writing – review & editing. **Fatjona Kraja:** Data curation, Writing – original draft, Formal analysis, Writing – review & editing. **Gustavo Nader Marta:** Investigation, Data curation, Writing – review & editing, Formal analysis, Project administration, Resources, Writing – review & editing. **Wellington Furtado Pimenta Neves Junior:** Data curation, Formal analysis, Writing – review & editing. **Gustavo Viani de Arruda:** Data curation, Writing – review & editing. **Andre Guimaraes Gouveia:** Data curation, Writing – review&editing. **Pierfrancesco Franco:** Writing – review & editing, **Philip Poortmans:** Writing – review & editing, **Ivica Ratosa:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Project administration, Resources, Software, Writing – review&editing.

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Appendix A. Supplementary data

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