



## Systematic Review

## Exposure of the oesophagus in breast cancer radiotherapy: A systematic review of oesophagus doses published 2010–2020



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## ABSTRACT

**Background and purpose:** Breast cancer radiotherapy can increase the risk of subsequent primary oesophageal cancer, with risk increasing according to oesophagus radiation dose. We describe oesophagus exposure from modern breast cancer regimens and discuss the risks of oesophageal cancer for women irradiated recently.

**Materials and methods:** A systematic review was undertaken of oesophagus doses from breast cancer radiotherapy regimens published during 2010–2020. Mean and maximum oesophagus doses were described for different target regions irradiated and different radiotherapy techniques.

**Results:** In 112 published regimens from 18 countries, oesophagus doses varied with target region. For partial breast irradiation, average mean oesophagus dose was 0.2 Gy (range 0.1–0.4) in four regimens; maximum dose was not reported. For breast or chest wall radiotherapy, average oesophagus doses were mean 1.8 Gy (range 0.1–10.4) in 24 regimens and maximum 6.7 Gy (range 0.4–14.3) in seven regimens. For radiotherapy including a nodal region, average oesophagus doses were higher: mean 11.4 Gy (range <0.1–29.3) in 61 regimens and maximum 34.4 Gy (range 3.4–51.3) in 55 regimens. Average mean oesophagus doses were >10 Gy for intensity modulated nodal radiotherapy, but lower for other node techniques.

**Conclusions:** Mean oesophagus doses from partial breast and breast/chest wall regimens were usually less than 2 Gy, hence radiation-risks will be very small. However, for radiotherapy including lymph nodes, average mean oesophagus dose of 11.4 Gy may nearly double oesophageal cancer risk. Consideration of oesophageal exposure during nodal radiotherapy planning may reduce the risks of radiation-related oesophageal cancer for women irradiated today.

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Breast cancer is the most prevalent cancer in many countries worldwide and it is estimated that one in eight women will be diagnosed with it during their lifetime in high-income countries [1–3]. Most women are diagnosed when the disease is at an early stage. Survival has improved recently, and the 10-year survival for non-metastatic breast cancer is now 84% in the USA [3]. The increasing numbers of women surviving breast cancer long-term mean it is important to consider the late effects of treatment.

Most women diagnosed with early breast cancer receive adjuvant radiotherapy [1]. Radiotherapy reduces the risk of breast cancer mortality for women after breast conserving surgery and for

women after mastectomy for node-positive disease [4,5]. These radiotherapy benefits need to be balanced against the risks. Randomised trials have identified heart disease, lung cancer and oesophageal cancer as the main diseases where breast cancer radiotherapy can increase the mortality risk [6]. The radiation-related risks of these diseases depend on the incidental doses received by the heart, lungs and oesophagus respectively [6–8].

The risks for women being considered for radiotherapy today are likely to be lower than for the women irradiated in the randomised trials. This is because the women in these trials were irradiated many years ago. Radiotherapy can be delivered more precisely now than it was in the past, and the doses to the heart, lungs and oesophagus from typical modern radiotherapy are likely to be lower. To assess the risks from modern radiotherapy, published dose–response relationships can be combined with typical modern organ doses to provide estimates of the proportional

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increase in risk from typical modern radiotherapy regimens. Organ doses from breast cancer radiotherapy regimens vary substantially according to geographical region, target regions irradiated, technique and other factors. Therefore, when assessing the risks from modern radiotherapy, it is necessary to consider the totality of the published dosimetry evidence, rather than doses from specific regimens or publications.

For heart disease and lung cancer, both dose–response relationships and systematic reviews of heart and lung doses from modern regimens are available [6–10]. These can be used to estimate the proportional risks of heart disease and lung cancer from modern breast cancer regimens. For oesophageal cancer, a number of observational studies have shown increased oesophageal cancer risk after radiotherapy [11–14]. A dose–response relationship based on 252 women who developed oesophageal cancer after breast cancer radiotherapy suggests that the risk of oesophageal cancer increases by 7.1% per Gy (95% confidence interval 1.9–20.6) median oesophagus dose [8]. However, at present no systematic reviews of oesophageal dose from modern breast cancer radiotherapy have been conducted. If average oesophagus doses from modern radiotherapy were systematically reviewed and summarised, these doses could be combined with the dose–response relationship to estimate the typical risk of oesophageal cancer from modern regimens.

A systematic review of reported oesophagus doses would also provide information on the frequency of oesophagus dose reporting in breast cancer radiotherapy planning, relative to other organs such as heart or lungs. We present a systematic review of oesophagus doses from early breast cancer radiotherapy dosimetry studies published worldwide during 2010 to 2020. We describe variation in doses according to anatomical regions irradiated and techniques used, and discuss the likely risks of oesophageal cancer for women irradiated recently.

## Materials and methods

### Study eligibility criteria

Breast cancer radiotherapy dosimetry studies published between 1 January 2010 and 31 December 2020 that reported either mean oesophagus dose (dose averaged over the whole contoured oesophagus) or maximum oesophagus dose (maximum point doses or near maximum doses) to the whole oesophagus, were eligible for inclusion, regardless of whether the radiotherapy plans had been delivered (Fig. 1). As near maximum doses we included D2% (minimum dose to hottest 2% of organ) and D1cc or D5cc (minimum dose to hottest 1 cc or 5 cc of organ). All these measures were considered equivalent to maximum dose. Excluded studies were those that specified radiotherapy was given prior to 2010, studies of radiotherapy for advanced cancer or unresectable nodal disease, studies reporting data reported in another included study, studies reporting doses estimated using a phantom, and studies only reporting volumetric dose measures (e.g. V5, V10, V20, V30, V35, V40) to the whole oesophagus or reporting dose to the partial oesophagus only.

### Study identification

Studies were identified using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. EMBASE and SCOPUS were searched on 04 Jan 2021 using terms (“dos\* AND breast\* AND cancer\*/carcinoma\*/tumour\*/tumour\* AND radiation/radiotherapy”) to retrieve breast cancer radiotherapy studies published between 1 January 2010 and 31 December 2020. A broad search strategy was required, as studies do not necessarily

mention the oesophagus in their title, abstract or keywords.

### Data abstraction

The following information was sought for each study: author, year of publication, country of first author, treatment planning method, radiotherapy technique, beam energy and modality, use of breathing control, whether the radiotherapy plans were delivered, number of CT planning scans per regimen, breast cancer laterality, region(s) irradiated, prescription target dose and number of fractions (Tables S1 and S2). Oesophagus dose parameters extracted were the average, standard deviation and range for mean and maximum (or near maximum) oesophagus doses. Oesophagus volume parameters were not extracted for analyses because they were inconsistently or rarely reported.

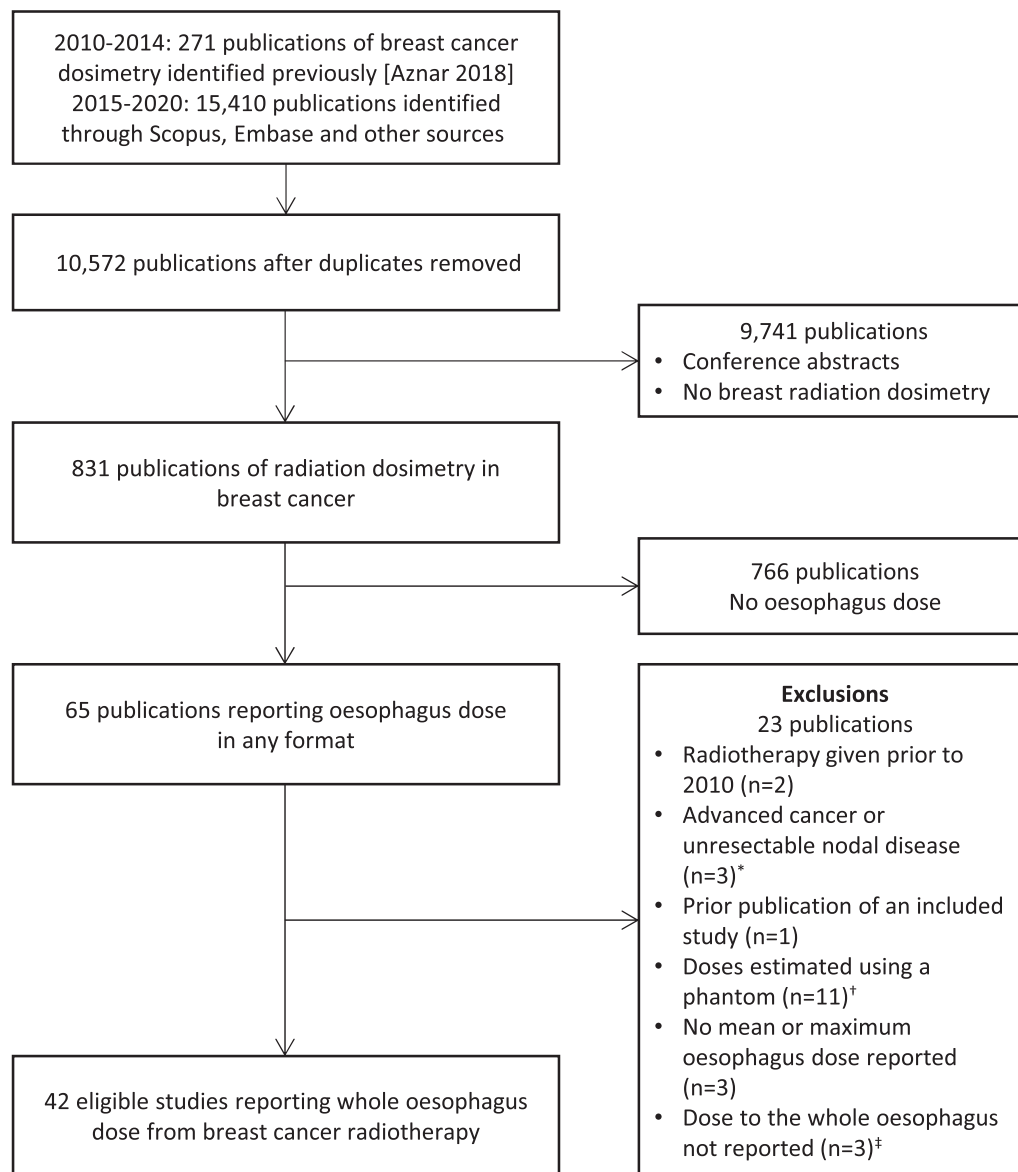
### Analyses

Analyses considered the average of the oesophagus dose measures from the CT plans included for each regimen described in each study. We term these the “average mean oesophagus dose” and the “average maximum oesophagus dose”. Oesophagus doses were compared between regions irradiated and radiotherapy techniques used. Variation in average doses within categories was assessed using chi-squared tests for heterogeneity, difference or trend.

## Results

There were 831 publications of radiation dosimetry in breast cancer during 2010–2020 and, of these, 42 from 18 countries reported mean or maximum doses to the whole oesophagus (Fig. 1). The total number of regimens reporting mean or maximum oesophagus doses was 112 (Table 1, Table S2, Text S1) with, on average, 26 CT plans per regimen (range 2–311). The number of regimens reporting oesophagus dose increased over time. None reported oesophagus dose during 2010–2012. Thereafter a few regimens were published per year, with a maximum of 25 regimens per year during 2020. Mean oesophagus dose was reported in 89 regimens. Maximum dose measures were reported in 62 regimens including Dmax (38 regimens), D2% (21 regimens), D5cc (2 regimens) and D1cc (1 regimen). Physical dose measures were used in 41/42 studies and used in the analyses. It was not possible to calculate equivalent dose in 2 Gy per fraction (EQD2) accurately as dose volume histograms for the oesophagus from the individual radiotherapy plans were not provided in the published studies. One study by Santos et al (Table S2, Text S1) compared different dose fractionation schedules and only reported biological doses. In this study the reported doses were low, and the difference between physical and biological was judged to be negligible. In all included studies, the total dose per fraction used was 2 Gy, 2.7 Gy, 1.8 Gy, 3.5 Gy, 1.7 Gy and not specified for 58% (65/112), 19% (21/112), 18% (20/112), 4% (4/112), 1% (1/112) and 1% (1/112) of regimens respectively (Table S2). For mean oesophagus dose, most regimens were for left breast cancer ( $n = 51$ ) or had laterality unspecified ( $n = 26$ ). Few regimens reported dose from right breast cancer ( $n = 9$ ) or bilateral breast cancer ( $n = 3$ ). Four studies included patients classified as having atypical anatomy i.e. unfavourable cardiopulmonary anatomy [16,17], large body habitus or breast volume [18], or breast reconstruction [19]. As such factors were unlikely to lead to atypical oesophageal exposure, these four studies were included.

Average mean oesophagus dose was 8.3 Gy overall, with a wide range of regimen-specific doses from 0.1 to 29.3 Gy (Table 1). Average mean doses were higher in left radiotherapy



**Fig. 1.** The process of study identification for the review. \* Advanced disease was metastatic disease outside the breast/nodal regions. † Dose was calculated using an anatomical phantom, not using patient CT-planning scans ‡ One study contoured the oesophageal inlet only, another study contoured just the cervical oesophagus.

than right radiotherapy (10.1 versus 1.7 Gy) but most of the left regimens included the nodes, whereas none of the right regimens did. Regimen-specific doses were grouped into 5 Gy categories (Fig. 2). For mean dose (Fig. 2a) the commonest category was the lowest (<5 Gy): 40/89 regimens (45%). Mean doses of 15 Gy or more were delivered for only 17/89 (19%) of regimens. For maximum oesophagus dose (Fig. 2b) the commonest categories with 13 regimens each were 40–45 Gy and 45 + Gy but there was substantial variation, with some regimens in every 5.0 Gy category from <5 to 45 + Gy.

Average mean oesophagus dose in 89 regimens was 8.3 Gy, with standard error (SE) 0.9, and range 0.1–29.3 (Table 1, Fig. 3). Average regimen dose increased according to regions irradiated. For partial breast it was 0.2 Gy (SE 0.1) based on 4 regimens, for breast or chest wall it was 1.8 Gy (SE 0.5) based on 24 regimens and for breast or chest wall with SCF (supraclavicular fossa)/axilla ± internal mammary chain (IMC) it was 11.4 Gy (SE 1.1) based on 61 regimens,  $2p < 0.001$  for trend across regions irradiated. Only 32/89 of these regimens were actually delivered to patients but average

exposure of the oesophagus was similar according to regions irradiated and technique used for these regimens. (Fig S1).

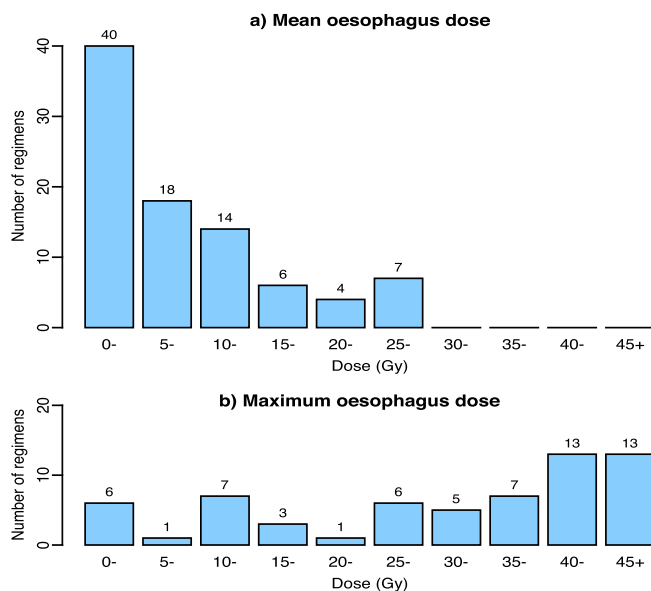
Within regions irradiated, oesophagus doses varied according to radiotherapy technique (Table S1, Fig. 3). For partial breast, anterior direct/oblique fields gave 0.1 Gy (SE 0.0), and brachytherapy regimens gave 0.4 Gy (SE 0.0). For breast or chest wall radiotherapy, tangents (± field-in-field (FIF)), static field IMRT and rotational IMRT (VMAT or Tomotherapy) were used. Technique-specific average mean oesophagus dose was 0.4 Gy (SE 0.0) for static field IMRT, 1.0 Gy (SE 0.4) for tangents (± FIF) and 2.9 Gy (SE 1.0) for rotational IMRT. For breast or chest wall with SCF/axilla ± IMC, hybrid techniques (a combination of tangents and rotational IMRT), PBS (pencil beam scanning) protons, tangents (± FIF) and static and rotational IMRT were used. Technique-specific doses varied from 6.9 Gy (SE 0.6) for hybrid regimens to 17.5 Gy (SE 2.1) for static field IMRT. Oesophageal exposure did not increase with the use of IMC irradiation (mean oesophageal dose breast or chest wall with SCF/Axilla: 14.1 Gy (SE 1.8), mean oesophageal dose breast or chest wall with SCF/Axilla and IMC: 8.8 Gy (SE 1.0) (Fig. S2).

**Table 1**

Studies reporting oesophagus dose from breast cancer radiation therapy regimens published 2010–2020.

Breast cancer laterality	Dose measure <sup>a†</sup>	No. of studies	No. of regimens		No. of CT plans per regimen <sup>§</sup>		Oesophagus Dose (Gy)	
			Total	Nodal RT <sup>‡</sup>	Average	Range	Average	Range
Left <sup>*</sup>	Mean	17	51	38	14	4–50	10.1	<0.1–29.3
	Max	9	27	26	11	4–35	31.1	3.4–48.2
Right <sup>*</sup>	Mean	4	9	0	15	2–43	1.7	<0.1–10.4
	Max	2	2	1	22	10–35	20.4	12.9–28.0
Bilateral	Mean	2	3	1	9	5–16	3.5	2.0–6.4
	Max	2	2	2	15	14–16	28.0	12.9–43.1
Unspecified <sup>  </sup>	Mean	14	26	22	65	4–311	7.8	0.3–15.0
	Max	15	31	26	39	3–311	32.4	0.4–51.3
All studies reporting mean dose		33	89	61	29	2–311	8.3	<0.1–29.3
All studies reporting max dose		26	62	55	25	3–311	31.3	0.4–51.3
<b>All studies<sup>**</sup></b>		<b>42</b>	<b>112</b>	<b>79</b>	<b>26</b>	<b>2–311</b>	–	–

Abbreviations: RT: radiotherapy; CT: computerised tomography; Gy: gray

<sup>a†</sup>Physical dose measures were reported in 41/42 studies and were used for quantitative analyses. Santos et al. (Table S2, Text S1) only reported biological doses but doses were low, and the difference between physical and biological was judged to be negligible.<sup>‡</sup>Maximum oesophagus doses included point doses or near maximum doses to the whole oesophagus.<sup>§</sup>Regimens included irradiation of any nodal region such as supraclavicular fossa, axilla or internal mammary chain.<sup>§</sup>The number of CT plans created per regimen<sup>\*</sup>Some studies reported doses from both left-sided and right-sided regimens and so contribute to both rows.<sup>||</sup>Studies did not report dose measures separately by laterality.<sup>\*\*</sup>Represents the number of unique studies which reported either mean oesophagus dose, max oesophagus dose, or both mean and max doses.**Fig. 2.** Distribution of average mean and maximum oesophagus doses from breast cancer radiotherapy regimens published during 2010–2020.

The average maximum oesophagus dose was 31.3 Gy (SE 1.9) with range 0.4 to 51.3 Gy. It increased according to regions irradiated (Fig. 4). For partial breast radiotherapy, no regimens reported maximum oesophagus dose. For breast or chest wall maximum oesophagus dose was 6.7 Gy (SE 2.2) based on 7 regimens, and for breast or chest wall and SCF/axilla  $\pm$ IMC it was 34.4 Gy (SE 1.7) based on 55 regimens ( $2p < 0.001$  for difference). Within regions irradiated, maximum dose varied according to technique. For breast or chest wall radiotherapy, there were only one to two regimens per technique. The average maximum dose varied from 0.7 Gy (SE 0.3) for tangents to 13.6 Gy (SE 0.7) for hybrid techniques (combined tangents/rotational IMRT). For breast or chest wall with SCF/axilla  $\pm$  IMC, technique-specific averages were all above 27.0 Gy, and they varied from 27.2 Gy in one hybrid regimen to 44.0 Gy (SE 1.1) for static field IMRT. Oesophageal exposure did

not increase with the use of IMC irradiation (maximum oesophageal dose breast or chest wall with SCF/Axilla: 35.1 Gy (SE 3.1), maximum oesophageal dose breast or chest wall with SCF/Axilla and IMC: 33.9 Gy (SE 1.9) (Fig. S3).

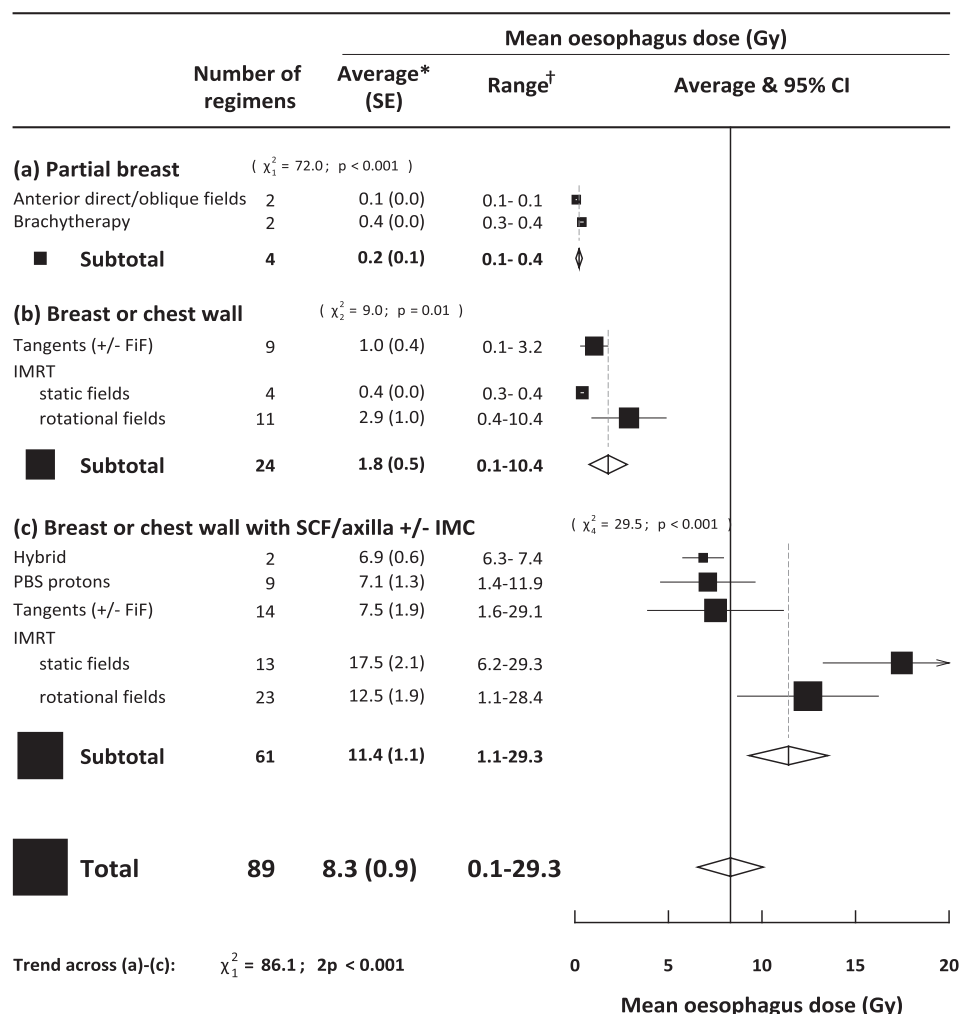
## Discussion

This systematic review of oesophagus doses from breast cancer radiotherapy regimens published during 2010–2020 shows that oesophageal exposure from breast cancer radiotherapy varied widely, but with clear evidence of several factors influencing it systematically. The main determinant of both mean and maximum oesophagus dose was inclusion of lymph nodes. Most partial breast and breast or chest wall regimens delivered less than 2.0 Gy mean dose. In contrast, regimens that irradiated the nodes delivered more than 10.0 Gy average mean dose, with the highest doses coming from IMRT. There was no evidence that oesophageal exposure was increased by inclusion of the IMC.

Oesophagus dose is reported infrequently compared with heart and lung doses, suggesting that it may not be routinely considered in radiotherapy planning. Only 5% (42/831) of breast cancer radiotherapy dosimetry studies published during 2010–2020 reported oesophagus dose. This compares to 73% (198/271) of breast cancer radiation dosimetry studies published during 2010–2015 reporting lung dose [10] and 60% (167/277) of studies published during 2003–2013 reporting heart dose [9].

This is the first systematic review of oesophagus exposure from modern breast cancer radiotherapy. It has several strengths. First, data on regimens and doses were abstracted by a radiation oncologist, and checked by two physicists. Second, there was a wide search strategy so it is likely that all relevant studies were identified. Third, it includes data from 112 regimens in 42 studies published in 18 countries, enabling estimation of the effects of both target and technique on oesophagus doses.

A limitation is that this review may not represent routine breast cancer practice. This is reflected by the fact that 81/112 (72%) of the regimens reported involved advanced techniques including IMRT and PBT. Although these more advanced techniques are emerging as routine practice in many centres internationally



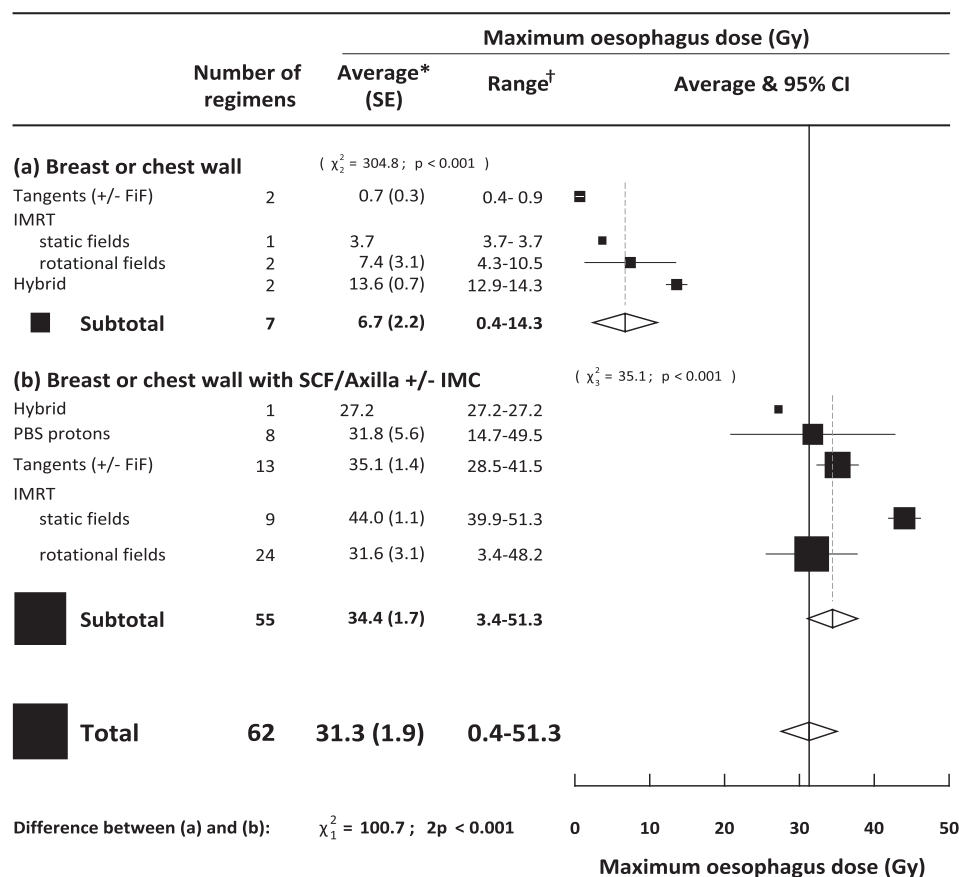
**Fig. 3.** Mean oesophagus dose from breast cancer radiotherapy according to regions irradiated and technique used. Abbreviations: Gy: gray; SE: standard error; CI: confidence interval; FiF: field-in-field (multiple segments); IMRT: intensity modulated radiotherapy; PBS: pencil beam scanning; SCF: supraclavicular fossa; IMC: internal mammary chain. Technique definitions are provided in Table S1 X2 and p values are for heterogeneity. \*Average of mean oesophagus doses for reported regimens. †Range of mean oesophagus doses for reported regimens.

[20,21] and it is important to consider oesophagus exposure in emerging techniques, 3D-conformal tangential techniques remain the most commonly used techniques today in many countries. Most studies do not provide information on reasons for dosimetric study e.g. research, new protocol, evaluation of routine practice. We were therefore unable to assess whether these regimens were considered routine in reporting centres. We were able to assess exposure of the oesophagus for regimens actually delivered. This was similar according to region irradiated and technique to exposure when accounting for both regimens delivered and not delivered. Another limitation is that instructions for oesophagus contouring were rarely described in the studies. The extent of cranial and caudal contouring may have varied between studies, which would increase inter-study variability, especially for mean oesophagus dose. In many studies, detailed descriptions of radiotherapy planning were also lacking. Therefore, it was not possible to investigate if certain radiotherapy planning factors systematically influenced oesophagus exposure, for example, the effect of delivering treatment with the gantry head straight versus rotated, or of using different gantry angles for the supraclavicular fossa field. Finally, our study provides a summary of the average doses from various regimens, not individual patient doses. In most included regimens, oesophagus doses varied substantially between

individual patients. For example, in the study with the largest number of patients per regimen, 311 patients received one radiotherapy regimen, 3D-conformal tangents to the breast/chest wall and regional lymph nodes. The average mean oesophagus dose in these 311 patients was 7.3 Gy but the standard deviation was 4.8 Gy. [22]. Hence this review cannot be used to estimate doses for individual patients.

In breast or chest wall radiotherapy, mean oesophagus doses were usually less than 2.0 Gy. This is likely to be because the oesophagus is located in the midline, posteriorly in the chest and is therefore rarely included in breast or chest wall fields. In contrast, the oesophagus is located adjacent to the supraclavicular fossa and behind the internal mammary nodes, so fields used to treat these nodes may exit through it, particularly when rotational IMRT is used. The oesophagus is often close to field edges, so small changes to field boundaries or angles, can cause substantial changes to oesophagus dose. In a study of 414 women irradiated for breast cancer during 1943–1996, the location of the supraclavicular field border relative to the midline was a key determinant of oesophagus dose [11]. During the 1980s and 1990s, breast cancer radiotherapy was usually field-based, and the medial border was usually placed off the midline, with the oesophagus out of the field [23]. It is now standard practice to contour the supraclavicular





**Fig. 4.** Maximum oesophagus dose from breast cancer radiotherapy according to regions irradiated and technique used. Abbreviations: Gy: gray; SE: standard error; CI: confidence interval; FiF: field-in-field (multiple segments); IMRT: intensity modulated radiotherapy; PBS: pencil beam scanning; SCF: supraclavicular fossa; IMC: internal mammary chain Technique definitions are provided in Table S1 X2 and p values are for difference. Footnotes to Figure 4. \*Average of maximum oesophagus doses for reported regimens. †Range of maximum oesophagus doses for reported regimens.

fossa nodal region using international atlas guidelines [24–26]. In an era of volume-based planning the medial border may now be placed more medially to cover contoured volumes, so the oesophagus may more often be included in the fields.

In nodal radiotherapy, IMRT resulted in higher oesophagus doses than 3D-conformal tangents or protons. This may be because multiple beam angles can result in a “low dose bath” which includes the oesophagus. It may also reflect the lack of dose constraints on the oesophagus during optimisation. Few studies compared static and rotational IMRT in the same patients [18,27–31] and in the 36 nodal IMRT regimens reporting mean oesophageal dose, beam angles and arc spans varied widely. Hence, differences between static and rotational IMRT in our study may be due to individual planning choices rather than type of IMRT (static *versus* rotational) per se.

These doses may be used to estimate average risks from different regimens by combining them with a published dose–response relationship in which the excess relative risk of oesophageal cancer increased by 7.1% per Gy for both median and mean oesophagus dose [8]. In our dose review, partial breast or breast/chest wall radiotherapy usually delivered mean oesophagus dose of <2.0 Gy. However, radiotherapy including the nodes delivered average mean oesophagus dose 11.4 Gy. Applying 7.1% per Gy, a dose of 11.4 Gy would increase the oesophageal cancer relative risk by 81% ( $7.1 \times 11.4 = 80.9$ ) i.e. it would nearly double the risk.

Radiation-related risk from 2010 to 2020s breast cancer radiotherapy may also be estimated by comparing the oesophagus doses in this review with doses received by women in past randomised

trials. In an individual patient data meta-analysis of around 40,000 women in 75 randomised trials, breast cancer radiotherapy approximately doubled the rate ratio for oesophageal cancer (RR = 2.42 95%CI 1.19–4.92) [6]. The average mean oesophagus dose received by women in the trials was 8.4 Gy, which is similar to the average dose of 11.4 Gy from node radiotherapy in our review. This comparison of doses also suggests that breast cancer nodal radiotherapy delivered during 2010–2020 may approximately double the relative risk of oesophageal cancer.

The future lifetime risk of oesophageal cancer for women aged 60 in the general population is about 0.2% in the USA and 0.7% in the UK [32]. If women receive typical breast cancer nodal radiotherapy with 11.4 Gy oesophagus dose, then this risk may be approximately doubled [8]. Smoking increases the risk of oesophageal cancer, and the ratio of the age-specific mortality rates for women in the UK who currently smoke, compared to that for women who have never smoked is about three [33]. Hence the radiation-risks would also be higher in smokers than in non-smokers.

Oesophageal contouring is time-consuming, and guidelines are lacking. This is important, since the mean dose will depend on the length of oesophagus contoured. For a few women at high risk of oesophageal cancer e.g. current smokers who require IMRT to the regional lymph nodes, contouring and consideration of oesophageal exposure may help to reduce their risks of radiation-related oesophageal cancer. However, for most women being considered for breast cancer radiotherapy today, the absolute excess oesophageal cancer radiotherapy-risks are likely to be <1% and are likely outweighed by the benefits.

## Conflicts of interest

None.

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## Data Sharing

The data sharing policy is available online: <https://www.ndph.ox.ac.uk/data-access>.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2021.09.032>.

## References

- [1] DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014;64:252–71. <https://doi.org/10.3322/caac.21235>.
- [2] Cancer Research UK. Cancer Statistics for the UK, <https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk>; 2019 [accessed 05-Jun-2019].
- [3] American Cancer Society. Breast Cancer Facts and Figures 2019–2020. Atlanta, Ga: American Cancer Society; 2020.
- [4] Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–16. [https://doi.org/10.1016/S0140-6736\(11\)61629-2](https://doi.org/10.1016/S0140-6736(11)61629-2).
- [5] Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127–35. [https://doi.org/10.1016/S0140-6736\(11\)61629-2](https://doi.org/10.1016/S0140-6736(11)61629-2).
- [6] Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017;35:1641–9. <https://doi.org/10.1200/JCO.2016.72.0722>.
- [7] Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–98. <https://doi.org/10.1056/NEJMoa1209825>.
- [8] Journe N, Schonfeld SJ, Hauptmann M, Roberti S, Howell RM, Smith SA, et al. Dose-volume effects of breast cancer radiation therapy on the risk of second oesophageal cancer. *Radiation Oncol* 2020;15:133–9. <https://doi.org/10.1016/j.radonc.2020.07.022>.
- [9] Taylor CW, Wang Z, Macaulay E, Jaggi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiation therapy: a systematic review of heart doses published during 2003 to 2013. *Int J Radiat Oncol Biol Phys* 2015;93:845–53. <https://doi.org/10.1016/j.ijrobp.2015.07.2292>.
- [10] Aznar MC, Duane FK, Darby SC, Wang Z, Taylor CW. Exposure of the lungs in breast cancer radiotherapy: a systematic review of lung doses published 2010–2015. *Radiation Oncol* 2018;126:148–54. <https://doi.org/10.1016/j.radonc.2017.11.022>.
- [11] Lamart S, Stovall M, Simon SL, Smith SA, Weathers RE, Howell RM, et al. Radiation dose to the esophagus from breast cancer radiation therapy, 1943–1996: an international population-based study of 414 patients. *Int J of Radiat Oncol Biol Phys* 2013;86:694–701. <https://doi.org/10.1016/j.ijrobp.2013.03.014>.
- [12] Morton LM, Gilbert ES, Hall P, Andersson M, Joensuu H, Vaalavirta L, et al. Risk of treatment-related esophageal cancer among breast cancer survivors. *Ann Oncol* 2012;23:3081–91. <https://doi.org/10.1093/annonc/mds144>.
- [13] Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients. *Radiation Oncol* 2015;114:56–65. <https://doi.org/10.1016/j.radonc.2014.10.004>.
- [14] Grantzau T, Overgaard J. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: A systematic review and meta-analysis of population-based studies including 522,739 patients. *Radiation Oncol* 2016;121:402–13. <https://doi.org/10.1016/j.radonc.2016.08.017>.
- [15] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339: b2535. 10.1136/bmj.b2535.
- [16] Cendales R, Schiappacasse L, Schnitman F, García G, Marsiglia H. Helical tomotherapy in patients with breast cancer and complex treatment volumes. *Clin Transl Oncol* 2011;13:268–74. <https://doi.org/10.1007/s12094-011-0652-2>.
- [17] Cuaron JJ, Chon B, Tsai H, Goenka A, DeBlois D, Ho A, et al. Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *Int J Radiat Oncol Biol Phys* 2015;92:284–91. <https://doi.org/10.1016/j.ijrobp.2015.01.005>.
- [18] Pasler M, Georg D, Bartelt S, Lutterbach J. Node-positive left-sided breast cancer: does VMAT improve treatment plan quality with respect to IMRT? Linkseitiges Mammakarzinom inklusive Lymphabfluss: Verbessert VMAT die Planqualität gegenüber IMRT? *Strahlenther Onkol* 2013;189:380–6. <https://doi.org/10.1007/s00066-012-0281-2>.
- [19] Dumane VA, Saksornchai K, Zhou Y, Hong L, Powell S, Ho AY. Reduction in low-dose to normal tissue with the addition of deep inspiration breath hold (DIBH) to volumetric modulated arc therapy (VMAT) in breast cancer patients with implant reconstruction receiving regional nodal irradiation. *Radiat Oncol* 2018;13:187. <https://doi.org/10.1186/s13014-018-1132-9>.
- [20] Dundas KL, Pogson EM, Batumalai V, Boxer MM, Yap ML, Delaney GP, et al. Australian survey on current practices for breast radiotherapy. *J Med Imaging Radiat Oncol* 2015;59:736–42. <https://doi.org/10.1111/1754-9485.12348>.
- [21] Chowdhary M, Lee A, Gao S, Wang D, Barry PN, Diaz R, et al. Is proton therapy a “Pro” for breast cancer? A comparison of proton vs. non-proton radiotherapy using the national cancer database. *Front Oncol* 2019;14:678. 10.3389/fonc.2018.00678.
- [22] Yaney A, Ayan AS, Pan X, Jhawar S, Healy E, Beyer S, et al. Dosimetric parameters associated with radiation-induced esophagitis in breast cancer patients undergoing regional nodal irradiation. *Radiation Oncol* 2021;155:167–73. <https://doi.org/10.1016/j.radonc.2020.10.042>.
- [23] Hoskin P, editor. External Beam Radiotherapy (Radiotherapy in Practice). Oxford UK: Oxford University Press; 2006.
- [24] NRG Oncology. Breast Cancer Atlas <https://www.nrgoncology.org/ciro-breast> [accessed 09 April 2021].
- [25] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiation Oncol* 2015;114:3–10. <https://doi.org/10.1016/j.radonc.2014.11.030>.
- [26] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Sola AB, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. *Radiation Oncol* 2016;118:205–8. <https://doi.org/10.1016/j.radonc.2015.12.027>.
- [27] Badakhshi H, Kaul D, Nadobny J, Wille B, Sehoul J, Budach V. Image-guided volumetric modulated arc therapy for breast cancer: a feasibility study and plan comparison with three-dimensional conformal and intensity-modulated radiotherapy. *Br J Radiol* 2013;86:20130515. <https://doi.org/10.1259/bjr.20130515>.
- [28] Sugie C, Manabe Y, Hayashi A, Murai T, Takaoka T, Hattori Y, et al. Efficacy of the dynamic jaw mode in helical tomotherapy with static ports for breast cancer. *Technol Canc Res Treat* 2015;14:459–65. <https://doi.org/10.1177/1533034614558746>.
- [29] Teke F, Doğan MH, Kaya MA, Gümüş M. Dosimetric comparison of TomoDirect and TomoHelical plans in post-mastectomy chest wall radiation therapy. *Int J Radiat Res* 2017;15:259–66. 10.18869/acadpub.ijrr.15.3.259.
- [30] Wang J, Yang Z, Hu W, Chen Z, Yu X, Guo X. Intensity modulated radiotherapy with fixed collimator jaws for locoregional left-sided breast cancer irradiation. *Oncotarget* 2017;8:33276–84.
- [31] Zhao H, He M, Cheng G, Han D, Wu N, Shi D, et al. A comparative dosimetric study of left sided breast cancer after breast-conserving surgery treated with VMAT and IMRT. *Radiat Oncol* 2015;10:123. <https://doi.org/10.1186/s13014-015-0531-4>.
- [32] Radiation Risk Assessment Tool - Lifetime Cancer Risk from Ionizing Radiation <https://radiationcalculators.cancer.gov/radtrat/> Accessed 06 September 2021.
- [33] Pirie K, Peto R, Reeves GK, Green J, Bera V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet* 2013;381:133–41. [https://doi.org/10.1016/S0140-6736\(12\)61720-6](https://doi.org/10.1016/S0140-6736(12)61720-6).