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Estimating the risk of lung cancer and cardiac mortality from doses to the lung and heart from modern tangent-only breast radiotherapy

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Abstract

Purpose: The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that the risks of breast cancer treatment in woman smokers may outweigh the benefits. The data used doses from published reports using a variety of treatment techniques. In our study, the risks of lung cancer and heart disease were determined from a modern era tangential-only technique. *Methods and materials:* Doses to the lung and heart were obtained for tangential radiotherapy to the breast or chest wall. The risk of lung cancer incidence and cardiac mortality were calculated by taking the ratio of our doses to those published by the EBCTG. *Results:* A total of 77 women were identified meeting our inclusion criteria. The mean combined whole lung dose was 2·0 Gy. The mean whole heart dose was 0·9 Gy. The estimated risk of lung cancer and cardiac mortality in a 50-year-old life-long smoker was estimated to be 1·5 and <1%, respectively. *Conclusions:* Tangential only radiotherapy delivered substantially lower doses to the combined whole lung and whole heart than those reported by the EBCTCG. In this cohort, the risks of radiation induced lung cancer and heart disease are outweighed by the benefits of radiotherapy even in those that are smokers.

Introduction

Over the last 4 decades, radiation therapy has played an important role in the treatment of breast cancer. Randomised trials show a benefit to radiation therapy as part of breast conservation therapy [1–4] as well as in the adjuvant setting after mastectomy.[5–7] More recent randomised studies and large meta-analyses have expanded the role of radiotherapy in the adjuvant setting.[8–12]

It is been well established that exposure to therapeutic ionising radiation incurs a risk of radiation-induced carcinogenesis. In the setting of breast cancer treatment, prior studies have shown an increase in the incidence of lung cancer[13–17] and cardiac mortality.[18,19] Especially concerning is the increase in lung cancer incidence due to exposure of the lung to ionising radiation in patients that are smokers.[20]

An inherent difficulty in analysing long-term morbidity lies in the requirement of large datasets and in the unavoidability of the analysis being retrospective in nature. The first factor introduces an element of inhomogeneity as large datasets may require the pooling of diverse patients, techniques and doses. The second factor raises the issue of the analysis not being indicative of current practice methods.

Recently, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported on the estimated risks of radiation induced lung cancer as well as cardiac mortality in breast cancer patients treated with radiotherapy.[21] Their study analysed previously published reports regarding women treated for breast cancer either as part of breast conservation therapy or in the post-mastectomy setting. In brief, their calculation of the relative risk (RR) and excess relative risk (ERR) per Gray (Gy) for radiation induce lung cancer and cardiac mortality was based on the following: (1) studies reporting the subsequent incidence of lung cancer and cardiac mortality in women treated for breast cancer were reviewed. The dose to the adjacent lung and heart was estimated by recreating the portal arrangement on a representative patient phantom; (2) realising that the dose to the heart and lung may be different in the modern era, the EBCTCG then estimated the dose to the combined whole lung and heart by taking the unweighted average of doses to those organs during breast cancer therapy from studies published during 2010–2015; (3) using this data and the ERR for each organ, the risk of excess lung malignancy and cardiac mortality from radiotherapy were calculated. As an example, the EBCTCG estimated that the excess absolute risk of lung malignancy in a 50-year-old smoker treated for breast cancer as 4%. Therefore, the EBCTCG study raised concern that the excess radiation induced mortality may outweigh the benefits of mortality reduction by breast cancer treatment in this subset of women.

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However, the published reports from which the typical modern whole lung and heart doses were derived encompassed a variety of doses, treatment techniques and radiation modalities. This lack of uniformity may account for why the calculated typical modern whole lung and heart dose of 5·7 and 4·4 Gy, respectively, are much higher than the doses seen in modern practice for breast conservation therapy of early stage disease. Therefore, in turn, the risks as reported by the EBCTCG for cardiac mortality and lung malignancy in women smokers are higher and may be not be representative of those posed by techniques that minimise the dose to the heart and lung.

Nonetheless, the EBTCG publication still allows for an opportunity to assess the long-term risks involved in breast radiotherapy for a specific treatment geometry. It is reasonable to accept the values for the RR and ERR for lung malignancy and cardiac morality as derived by the EBCTG as these numbers are based on one of the largest datasets with long-term follow-up. By substituting in the dose to the whole lung and heart from a cohort of women treated with a uniform technique in the modern era, a better estimation can be made of the incidence of radiation induced lung malignancy and cardiac mortality for a single technique.

The objective of this study was to tabulate the doses to the lung and heart for a cohort of women treated at a single institution with modern radiotherapy tangential-only techniques without inclusion of the internal mammary nodes (IM). The risk of radiation induced lung cancer and heart disease in a 50-year female lifelong smoker was then calculated based on the mean whole lung dose and heart dose for this cohort of patients.

Methods and materials

A retrospective review was made of women who had undergone radiation therapy as either treatment to the breast during breast conservation therapy or adjuvant treatment to the chest wall in the community based setting. The mean cardiac dose as well as mean lung doses were calculated from dosimetry data obtained from actual patient treatment plans. The mean lung dose and cardiac dose were then used to derive the estimated risks for lung cancer and cardiac mortality.

Patient population

Data (Table 1) obtained from dosimetry plans on a cohort of women with breast cancer treated at our facility from years 2013 through 2016 was obtained. These were women with breast cancer treated with radiation therapy either to the whole breast or to the chest wall. In a small group of patients, irradiation of the axillary nodes was administered through the tangential fields. None of the included patients receive treatment to fields specifically designed to treat the IM nodes (e.g., 'wide-field' tangents). Data were available for the total prescribed dose, dose per fraction, mean whole lung dose, mean whole heart dose and mean dose–volume histogram (DVH) distribution for both lung and heart doses that was stratified with regards to ipsilateral and contralateral breast cancers.

Calculation of combined whole lung dose and whole heart dose

All the patients in our study were treated with tangential radiotherapy encompassing the breast or chest wall. None of the patient had portals designed to treat the IM nodes. In addition, if the axillary contents were to be treated, this was done through the use of a 'high' tangential port.

Table 1. Patent data

Number (*n*)	77
Age (years)	
Mean	60
Range (min–max)	34–84
Date (year)	
Range	2013–2016
Laterality of breast cancer	
Right	34
Left	43
Dose (Gy)	
Mean	56
Range (min–max)	40–66
Dose/fraction (Gy)	
Mean	2·1
Range (min–max)	2·0–2·5
Stage	
Tis	12
T1	34
T2	18
T3	5
T4	8
N0	54
N1	14
N2	9

The entire right lung, left lung and heart were identified as organs at risk (OAR) and were contoured using the Radiation Therapy Oncology Group contouring guidelines.[22] The dosimetry planning was done on either a Philips Pinnacle v9 (Andover, MA, USA) or Varian Eclipse VII (Palo Alto, CA, USA) treatment planning system.

The mean combined whole lung dose was determined by taking the unweighted average of the ipsilateral and contralateral whole lung dose. The whole heart dose was taken as the mean dose given to the entire heart volume.

The EBCTG study methodology

The first part of the EBCTCG study involved the calculation of the RR and ERR of lung malignancy and cardiac morality due to breast radiotherapy. This portion of the study involved the following: (1) a systematic review was made of doses, radiation field geometry, lung cancer incidence, and cardiac mortality from published randomised trials; (2) the portal geometry was reconstructed on a 'representative patient' phantom and the doses to

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the adjacent lung and heart were calculated; (3) the dose to the adjacent heart and lung were then coupled with the reported subsequent incidence of cardiac mortality and lung cancer, respectively, to calculate the RR and ERR per Gy for radiation induced lung cancer incidence and cardiac mortality.

The second part of the EBCTCG study involved the calculation of the dose to the lung and the heart due to breast cancer treatment in the modern era by taking the unweighted average of doses to these organs published during 2010–2015. These were termed the typical modern dose.

In the third part of the EBCTCG study, the ERR was combined with the typical modern dose delivered to the heart and lung to estimate the risks of lung cancer and cardiac mortality.[21,23]

Linear dose relationship

A linear dose relationship between dose and cardiac mortality and lung carcinogenesis was assumed by the authors of the EBCTG and accepted in our study as well as recent radiobiological data supports a linear relationship.[24,25] Furthermore, the acceptance of a linear dose relationship was reasonable due to the following: (1) the results of the EBCTG in terms of the absolute excess risk posed to women treated with radiotherapy was based on a linear dose relationship;[21,23] (2) the EBCTCG clearly recognised that lower doses to the heart and lung would proportionally reduce the risks;[21] (3) the results of our analysis could be compared with the results of the EBCTG without manipulation of the EBCTCG data that were not available to the authors of this study.

Calculation of estimated risk of lung cancer incidence

The calculation of the estimated risk of lung cancer was based on the following: (1) As noted in the EBCTCG study[21] and Supplement,[23] it was assumed that risk of lung cancer incidence is linearly dependent on the dose received by the combine whole lung; (2) the absolute risk of lung cancer incidence for a life-long women smoker receiving breast radiotherapy at the age of 50 was derived by taking the absolute risk as reported by the EBCTG of 4% and multiplying it by the ratio of our patient cohort's mean combined whole lung dose to the EBCTG study's reported mean combined whole lung dose of 5·7 Gy.

Calculation of Estimated risk of cardiac mortality

The calculation of the estimated risk of cardiac mortality was based on the following: (1) As noted in the EBCTG study[21] and Supplement,[23] it was assumed that risk of cardiac mortality is linearly dependent on the dose received by the whole heart; (2) the absolute risk of cardiac mortality for a life-long women smoker receiving breast radiotherapy at the age of 50 was derived by taking the absolute risk as reported by the EBCTG of 1% and multiplying it by the ratio of our patient cohort's mean whole heart dose to the EBCTG study's reported mean whole heart dose of 4·4 Gy.

Results

As shown in Table 2, a total of 77 women met our inclusion criteria. The mean whole lung dose for our cohort of patients was 3·8 Gy for the ipsilateral lung and 0·2 Gy for the contralateral lung.

Table 3 shows the dose to the ipsilateral lung, contralateral lung and heart separately for right sided and left sided breast cancer treatment. As to be expected, the dose to the contralateral lung is much lower than the dose to the ipsilateral lung regardless of laterality of breast cancer. Although not statistically significant the mean dose to the left lung as a result of left-sided breast treatment is higher than the dose to the right lung due to right-sided breast cancer treatment.

Tables 2 and 3 show the mean whole cardiac dose, cardiac dose from right-sided breast treatment and cardiac dose from left sided breast cancer as 0·9, 0·4, and 1·2 Gy, respectively.

Figures 1 and 2 show the mean lung and heart DVH plot as separated by laterality of breast treatment. Figure 3 shows the DVH plot of doses to the heart as a result of tangential breast therapy as a function of laterality of breast cancer treatment.

Table 4 shows the proportional reduction in risk for lung cancer incidence and cardiac mortality based on the underlying mean whole lung and cardiac doses.

Table 2. Whole lung and heart dose

	Dose (Gy)
Ipsilateral lung	
Mean	3·8
Range (min–max)	0·1–41·0
Contralateral lung	
Mean	0·2
Range (min–max)	0·0–2·7
Combined lung	
Mean	2·0
Heart	
Mean	0·9
Range (min–max)	0·1–14·3

Table 3. Lung and heart dose by laterality of breast cancer treatment

	Right breast	Left breast	*p*-value[a]
Ipsilateral lung			
Mean dose (Gy)	3·3	4·2	0·20
Range (min–max)	0·2–39·8	0·2–43·0	
Contralateral lung (Gy)			
Mean (Gy)	0·2	0·1	0·30
Range (min–max)	0·0–2·6	0·0–2·7	
Heart			
Mean (Gy)	0·4	1·2	0·001
Range (min–max)	0·0–3·7	0·1–23·1	

[a]*Note*: Welch's unpaired *t*-test

Discussion

Even in this most carefully tailored portal arrangement, the delivery of radiotherapy to the target incurs exposure of adjacent OAR to

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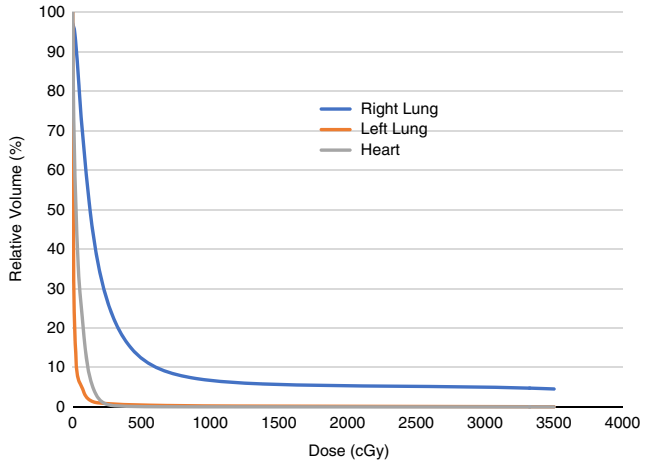

Figure 1. Dose–volume histogram for right lung, left lung and heart for right-sided tangential breast treatment.

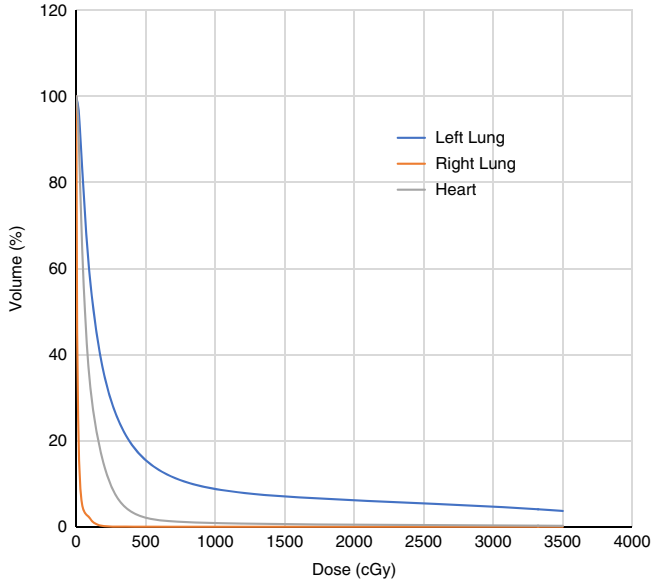

Figure 2. Dose–volume histogram for left lung, right lung and heart for left-sided tangential breast treatment.

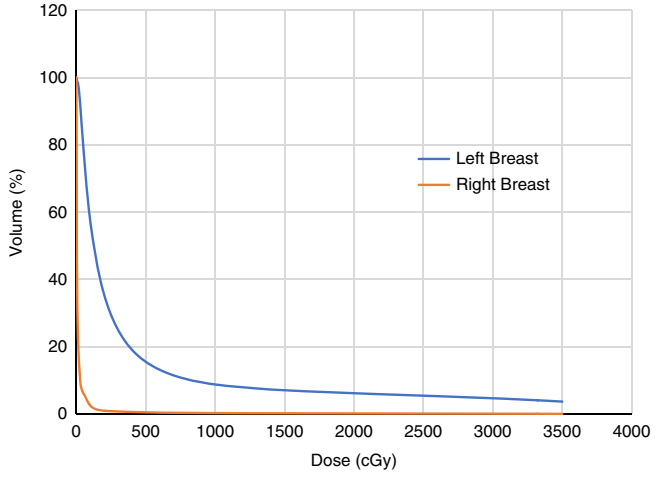

Figure 3. Dose–volume histogram (DVH) for heart depending on laterality of breast cancer.

Table 4. Excess increase in absolute risk of lung cancer incidence and cardiac mortality for a 50-year-old woman smoker based on underlying mean combined whole lung dose and mean cardiac dose[a]

	EBCTCG[21]		Current study	
	Organ mean dose (Gy)	Excess risk (%)	Mean dose (Gy)	Excess risk (%)
Lung cancer incidence	5·7	4	2·0	1·5
Cardiac mortality	4·4	2	0·9	<1

[a]*Note*: A linear relationship is assumed between dose exposure and incidence of lung cancer or cardiac mortality.

ionising radiation. This may lead to subsequent radiation-induced carcinogenesis or organ dysfunction. The risk is dependent on the dose received by the OAR and the OAR's inherent susceptibility to radiation-induced carcinogenesis or damage. The dose to the adjacent OAR is heavily dependent on the portal arrangement designed to deliver the prescribed dose to the target organ. Fortunately, this dose can be accurately calculated using today's treatment planning systems. The estimation of the risk of carcinogenesis and organ dysfunction requires long-term follow-up of a large number of patients. Most often, this requires the pooling of data from numerous treatment centres, therefore introducing an element of heterogeneity in the treatment techniques. Most importantly, given the long latency period between exposure and carcinogenesis, the calculated risks of radiation induced malignancy from retrospective analysis is representative of the effects of treatment techniques that may not be currently in use.

The risks of radiation exposure of the adjacent lung and heart are of particular concern in women treated with breast cancer. First, breast cancer is a very common disease with a paradigm shift occurring nearly 4 decades ago as women began being treated with breast conservation therapy rather than mastectomy.[1–4] The indications for adjuvant chest wall irradiation have been expanded as well.[8–12] Second, more women are being diagnosed with earlier stage breast cancer in which long-term survival is expected.[26,27] Third, data showing a marked increase in the incidence of lung cancer in smokers in other treated sites[14–16] raises the same concern in women smokers treated for breast cancer.[13,17]

The EBCTCG analysis incorporates a very large patient database that allows for a robust calculation of the ERR and RR regarding radiation-induced lung malignancy and cardiac mortality. However, the inhomogeneous treatment techniques on which this data is based may lead to an imprecise calculation of the risks posed by any one portal arrangement. Consequently, we attempted to address this issue by using the RR and ERR calculated by the EBCTCG as applied to a cohort of women uniformly treated for breast cancer by tangential portals alone.

In our cohort of women, the mean doses to the ipsilateral lung, contralateral lung and underlying heart in patients receiving breast radiotherapy using modern treatment planning and delivery were much lower than those recently reported by the EBCTCG. In our patient population, the mean doses to the ipsilateral lung, contralateral lung and heart were 3·8, 0·2 and 0·9 Gy, respectively. These doses are much lower than the estimated doses of 9·0 2·4 and 4·4 Gy delivered to the ipsilateral lung, contralateral lung and heart, respectively, as reported by the EBCTCG study.

It is reasonable to explain the difference in doses delivered to these organs in our patient cohort in the fact the only tangential

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radiation therapy fields were used and that none of the patients in the present study had radiation therapy fields designed to explicitly treat the IM nodes. However, a few patients had the supraclavicular and/or axillary nodes encompassed in the treatment fields. Therefore, the results are indicative of dose to the lungs and heart in patients treated with tangential field radiotherapy alone. As to be expected, tangential breast radiotherapy alone reduces the exposure to the lungs and heart.

As reported by others, the dose to the adjacent heart is dependent on the laterality of the treated breast.[28] The whole heart received a mean dose of 0·4 and 1·4 Gy during treatment of right-sided and left-side breast cancers, respectively.

In our cohort of women, although not reaching statistical significance, the mean dose to the ipsilateral left lung is slightly higher for left-sided breast treatment than doses to the ipsilateral right lung delivered by radiotherapy of right-sided breast cancers. Although, the right and left hemithorax are roughly equal in total volume, as a result of a portion of the volume of the left hemithorax being taken up the heart, the volume of the left lung is on average smaller than the right. Therefore, even with radiation portals identical in geometric configuration (with the exception of laterality), the left lung will incur a higher mean dose due to the lower overall volume.

As a result of the lower doses to the lung and heart in our cohort of women. We estimate the excess absolute risk for lung cancer due to tangential only radiotherapy in a lifelong women smoker receiving breast or chest wall radiation at the age of 50 is 1·5%. The excess risk of cardiac mortality in the same woman is <1%. This is lower than the excess absolute risk of 4 and 2% for lung cancer incidence and cardiac mortality, respectively, as recently reported by the EBCTCG study. Therefore, although not negligible, the risks from tangential only radiotherapy are low enough in which the benefit of mortality reduction due to the treatment outweighs the risks of treatment induced lung cancer and cardiac mortality even in this subset of women.

By calculating the dose to the heart and lung for a single treatment technique and by using actual patient records, the authors feel that our data represents an accurate estimation of the doses to the adjacent heart and lung incurred by tangential only breast or chest wall irradiation. However, the reliance on the EBTCG calculations of the RR and ERR still represents an inherent weakness in our study. Although we removed the inhomogeneity present in their derivation of the doses to the heart and lung delivered during treatment of breast cancer, our study still relied on the RR and RR as reported in the EBCTCG study which, in turn, were derived from reconstructing the portal arrangements on a 'representative patient phantom'. Therefore, their data were not derived from actual patient treatment plans. This inserts an inherent uncertainty between the calculated doses to the heart and lung and the actual doses delivered. The resolution would require reconstructing each individual treatment plan for the women in their study and clearly this is not feasible.

Conclusion

In conclusion, the doses delivered to the ipsilateral lung, contralateral lung and heart from modern day community-based tangential therapy alone are low and pose a very small risk with regards to lung cancer incidence and cardiac mortality even in women smokers. Therefore, having a strong smoking history should not be a contraindication to radiation therapy using a tangential-only technique.

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Conflicts of Interest. The authors have no conflict of interest to report.

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