


ORIGINAL ARTICLE

Is pectus excavatum a risk factor for radiation-induced lung disease in patients undergoing radiation therapy following breast-conserving surgery?

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Abstract

Background: The relationship between radiation dose to the ipsilateral lung and subsequent radiation-induced lung disease (RILD) in breast cancer patients with pectus excavatum (PE) undergoing radiation therapy (RT) to residual breast tissue after breast-conserving surgery has not yet been established. The incidence of RILD in such patients with PE, meaning that a large volume of the lung is within the radiation field, has not been determined. Therefore, the aim of this study was to determine the relationship between these factors.

Methods: The study cohort comprised 133 women who underwent three-dimensional conformal RT to residual breast tissue after breast-conserving surgery for breast cancer. Diagnoses of PE were based on Haller's, frontosagittal, and Monden's depression indices. Radiation doses to the ipsilateral lung were established from dose-volume histograms.

Results: Fifty of the 133 participants (37.6%) were diagnosed with RILD; all were asymptomatic. Multivariate analysis revealed a significant correlation between the incidence of RILD and the administration of > 30 Gy (V30). Surprisingly, although patients with PE received higher ipsilateral lung doses, they were less likely to develop RILD than those without PE.

Conclusions: Our data indicate that the incidence of RILD is correlated with the administration of > 30 Gy (V30) and that PE is not a risk factor for RILD after RT to residual breast tissue after breast-conserving surgery for breast cancer. Surprisingly, individuals with PE may have a lower incidence of RILD than those without this condition.

Introduction

Randomized trials and meta-analyses have shown that radiation therapy (RT) to all residual breast tissue after breast-conserving surgery in patients with early breast cancer reduces rates of local recurrence and mortality.^{1–4} Therefore, RT is widely administered to such patients in Japan – approximately 39 800 individuals annually – and the breast is the most frequently irradiated primary site.⁵ Three-dimensional conformal radiation therapy (3D-CRT) using two tangential beams is widely employed because

this approach provides good coverage of the target volume, that is, all residual breast tissue. However, because the radiation field to the breasts includes the lungs, correlations between radiation dose to the lungs and pulmonary complications have been extensively investigated.^{6–8} In particular, there is concern that the use of two tangential beams may increase the rates of pulmonary complications in patients with pectus excavatum (PE) because of the large volume of the lungs that lies within the radiation field. Accordingly, intensity modulated radiation therapy (IMRT)

and the lateral decubitus set-up technique have been developed to improve radiation delivery.^{9–12} However, studies in individuals with PE have estimated only the radiation dose to the lungs by constructing dose-volume histograms (DVHs). To the best of our knowledge, no published studies have investigated the incidence of pulmonary complications after the administration of 3D-CRT using two tangential beams. In this study, we therefore used computed tomography (CT) to investigate the relationship between radiation dose to the ipsilateral lung and subsequent radiation-induced lung disease (RILD) in women with and without PE undergoing RT to residual breast tissue after breast-conserving surgery for breast cancer. PE was diagnosed and assessed using various published indices.

Methods

Characteristics of the study participants

Of 263 women who underwent RT following breast cancer surgery in our hospital between January 2016 and March 2018, the 133 who subsequently received unilateral irradiation to residual breast tissue after breast-conserving surgery comprised the study cohort. Patients who underwent total mastectomy or received boost irradiation to the supraclavicular region or tumor bed were excluded. The Institutional Review Board of Nihon University School of Medicine approved this retrospective study and written informed consent was obtained from all participants.

Chest wall depression index

Computed tomography scanning with a slice thickness of 5 mm during free breathing was performed using an Aquilion TSX-201A (Toshiba Medical Systems, Tokyo, Japan). Data from axial CT images thus obtained were used to calculate the Haller index (HI), frontosagittal index (FSI), and Monden's depression index (MDI), which are established indices for assessing chest wall depression in individuals with PE. The following formulae were used (Fig 1):

- HI = maximum transverse diameter of the thorax (a)/distance between the posterior surface of the sternum and anterior border of the vertebral body at the point of maximum depression (b);¹³
- HI > 3.25 and HI > 3.1 separately reported as indications for surgical repair of PE;^{13,14}
- FSI = (b)/(a) × 100;¹⁵
- FSI < 28 and FSI < 33 separately reported as indications for surgical repair of PE;^{14,16}
- MDI = distance between the anterior surface of the sternum and anterior border of the vertebral body ipsilateral to the RT (c)/distance between the anterior borders of the frontal rib and dorsal rib (d).¹⁷

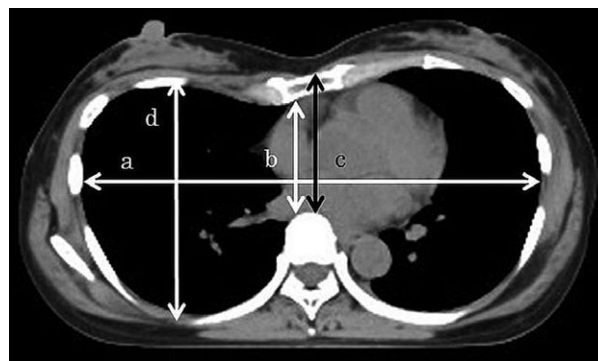


Figure 1 Computed tomography scan of a patient with pectus excavatum with a Haller index of 3.81, a frontosagittal index of 26.21, and a Monden's depression index of 0.533.

The mean MDI is reportedly 0.57 in healthy persons and 0.38 in patients with PE.¹⁷

Radiation therapy

Three dimensional-CRT consisting of two tangential beams was planned for all participants. The ipsilateral whole breast tissue was contoured with reference to findings on physical examination, Radiation Therapy Oncology Group Consensus Guidelines for anatomical borders for breast cancer,¹⁸ and contralateral whole breast tissue. It was planned that 95% of the prescribed dose would cover all ipsilateral breast tissue or at least the tumor bed. The lungs and heart were contoured and defined as organs at risk. The dosage to otherwise high-dose regions that would receive 107–110% of the prescribed dose was reduced using a field-in-field technique in all participants. Even if the individuals had PE, we obeyed the prescribed dose covering all ipsilateral breast tissue or the tumor bed. The treatment unit included a XiO Version 5.10 treatment planning system (Elekta CMS Software, Stockholm, Sweden) and Mevatron linear accelerator (Toshiba Medical Systems) using 4 MV photons. The prescribed total dose for all participants was 50 Gy in 25 fractions.

Dosimetric analysis

The percentages of the ipsilateral lung volume receiving more than 5, 10, 20, and 30 Gy (V5, V10, V20, and V30) were determined from DVHs using the Clarkson algorithm to assess the dose to the ipsilateral lung.

Evaluation of radiation-induced lung disease on computed tomography

Follow-up high-resolution CT images of 1 mm slice thickness were obtained during breath-holding and examined

for ground-glass opacities, consolidation, and increases in density. The following scoring system by Nishioka *et al.* was used, with Grade 1 or more being defined as RILD with an increase in density: Grade 0, no significant changes; Grade 1, pleural thickening only; Grade 2, pulmonary changes in < 50% of irradiated fields; and Grade 3, pulmonary changes in \geq 50% of irradiated fields.¹⁹ The first post-RT CT examination was performed at a median of 95 days (range: 7–480 days) after completion of RT. Typically, transient radiation pneumonitis and radiation fibrosis occur 4–12 weeks and 6–12 months after the completion of RT, respectively.²⁰ Patients who underwent their first post-RT CT examination < 50 days after completion of RT underwent a second CT examination at a median of 192 days (range: 93–504 days) after completion of RT. An increase in density was observed in all CT images of patients who underwent two or more CT examinations.

Statistical analysis

SPSS version 21.0 (IBM Corp., Armonk NY, USA) was used for statistical analysis. Univariate analyses using the Pearson's χ^2 test and multivariate analysis using stepwise logistic regression analyses were performed to determine associations of the following clinical factors with increase in density on CT images after completion of RT: age (< median vs. \geq median); hormonal treatment (yes vs. no); pre-RT chemotherapy (yes vs. no); chest wall depression indices: HI, FSI, and MDI (all < median vs. \geq median); and RT dosimetry (< median vs. \geq median). The relationship between the chest wall depression index (< median vs. \geq median) and dosimetry (< median vs. \geq median) was also evaluated by Pearson's χ^2 test. A *P* value of < 0.05 was considered statistically significant.

Results

The characteristics of the 133 patients are summarized in Table 1. Their median age at initiation of RT was 54 years (range: 35–83 years). The median HI was 2.74 (range: 1.64–4.1) and 28 (21.1%) patients had PE with HI > 3.1. The median FSI was 36.4 (range: 24.3–60.9) and 32 (24.1%) patients had PE with FSI < 33. The median MDI was 0.61 (range: 0.45–0.77) and 28 (21.1%) patients had HI > 3.1 and FSI < 33 and were accordingly diagnosed with PE, for which surgical repair was indicated.

The V5, V10, V20, and V30 of the ipsilateral lung are shown in Table 1. The median V20 was 10.2% (range: 0.9–15.3%).

Hormonal and trastuzumab treatment and RT were administered concurrently to 119 (89.5%) and 2 (1.5%)

Table 1 Characteristics of participants with pectus excavatum

Characteristics	N = 133
Age at RT (years)	54 (35–83)
Chest wall depression index	
Median HI	2.74 (1.64–4.1)
Median FSI	36.4 (24.3–60.9)
Median MDI	0.61 (0.45–0.77)
HI > 3.1 and FSI < 33	28 (21.1%)
Dose to the ipsilateral lung (%)	
Median V5	16.4 (4.9–22.8)
Median V10	13.4 (2.7–18.8)
Median V20	10.2 (0.9–15.3)
Median V30	7.6 (0.1–12.7)
Concurrent treatment	
Hormonal	119 (89.5%)
Trastuzumab \pm hormonal	2 (1.5%)
None	13 (9.8%)
Chemotherapy before RT	
Yes	12 (9.0%)
No	121 (91.0%)

FSI, frontosagittal index; HI, Haller index; MDI, Monden's depression index; RT, radiation therapy; Vx, percentage of a relative volume that received \times Gy.

patients, respectively. Chemotherapy was performed before RT in 12 (9.0%) patients.

An increase in density on CT images after completion of RT was found in 50 (37.6%) patients who were accordingly diagnosed with RILD. The increase in density did not extend outside the radiation field in any patient. None of the patients with radiation pneumonitis had respiratory symptoms that required treatment. Univariate analyses revealed no significant correlations between the incidence of RILD and HI, FSI, or MDI. In 28 patients diagnosed with PE for which surgical repair was indicated, only 7 patients were diagnosed with RILD. In the other 105 patients, 43 patients were diagnosed with RILD.

However, univariate analyses of DVHs revealed a significant correlation between the incidence of RILD and V5, V10, V20, and V30 values equaling or exceeding the median (*P* = 0.037, 0.030, 0.037, and 0.011, respectively). Multivariate analysis identified a significant correlation between the incidence of RILD and V30 values equaling or exceeding the median (*P* = 0.012) (Table 2). When relationships between chest wall depression indices and DVH were evaluated by univariate analysis, HI \geq median and FSI < median were strongly correlated with all V5 to V30 values \geq median of the dose to the ipsilateral lung, and MDI < median was strongly correlated with V20 and V30 values \geq median (Table 3). This indicates that all breast tissue was covered at higher ipsilateral lung doses, even in individuals with PE, because the ipsilateral lung dose was not intentionally reduced by using tangential beams at angles that would have resulted in poor coverage of all ipsilateral breast tissue.

Table 2 Correlations between listed factors and incidence of increase in CT density after RT

Characteristics	Univariate <i>P</i>	Multivariate <i>P</i> (95% CI)
Age (years) at RT	0.336	0.092
Chest wall depression index		
HI	0.946	0.411
FSI	0.946	0.469
MDI	0.771	0.353
Hormonal treatment at RT	0.946	0.866
Chemotherapy before RT	0.345	0.580
Dose to the ipsilateral lung		
V5	0.037*	0.890
V10	0.030*	0.965
V20	0.037*	0.383
V30	0.011*	0.012* (1.223–5.251)

*Value meets criterion for significance. CI, confidence interval; CT, computed tomography; FSI, frontosagittal index; HI, Haller index; MDI, Monden’s depression index; RT, radiation therapy; Vx, percentage of a relative volume that received × Gy.

Table 3 Results of univariate analyses of correlations between chest wall depression indices and doses derived from DVHs

Index	Dose to the ipsilateral lung	<i>P</i>
HI	V5 ≥ median	0.001*
	V10 ≥ median	0.004*
	V20 ≥ median	0.001*
	V30 ≥ median	0.001*
FSI	V5 ≥ median	0.001*
	V10 ≥ median	0.002*
	V20 ≥ median	0.001*
	V30 ≥ median	0.001*
MDI	V5 ≥ median	0.099
	V10 ≥ median	0.099
	V20 ≥ median	0.019*
	V30 ≥ median	0.007*

*Value meets criterion for significance. DVHs, dose-volume histograms; FSI, frontosagittal index; HI, Haller index; MDI, Monden’s depression index; RT, radiation therapy; Vx, percentage of a relative volume that received × Gy.

There were no correlations between an increase in density on CT images and age, tamoxifen use, or pre-RT chemotherapy.

Discussion

After comprehensive RT, 1–16% of patients with breast cancer and radiation pneumonitis reportedly have pulmonary symptoms,^{21–23} whereas the corresponding rate in those who undergo RT to the residual breast tissue alone, and not to the supraclavicular or other lymph nodes (with

the aim of limiting the radiation dose to the lungs), is 1–4%.^{6,7} None of the 133 patients in our series had symptoms of radiation pneumonitis. Asymptomatic RILD, including ground-glass opacities and consolidation, reportedly occurs in 78–90% of patients receiving RT to residual breast tissue after breast-conserving surgery,^{19,24} whereas it occurred in only 37.6% of our study cohort. Dosimetric predictors derived from DVHs have been studied for many years and it is widely known that the delivery of > 20 Gy to the lung is a predictor of radiation pneumonitis in patients with lung cancer.²⁵ Recently, however, it has been considered important to reduce the dose to V10 or V5.²⁶ In addition, in patients receiving RT to breast tissue, ipsilateral lung V10–40 is reportedly associated with the two-dimensional parameter of central lung depth and that delivery of > V25 to the lung is associated with an increase in density on CT images.^{8,24} It has also been reported that ipsilateral lung V20 > 35% is associated with symptomatic radiation pneumonitis when that RT includes the supraclavicular or other lymph nodes.⁶ The Radiation Therapy Oncology Group guidelines state that when administering RT to residual breast tissue alone, the ipsilateral lung dose should not exceed 15%.¹⁸

Pectus excavatum is the most common congenital chest wall deformity, with an incidence of 1 in 300–1000 births.²⁷ In one study, 3.7% of 273 patients who underwent RT to left breast tissue had clinically apparent PE.²⁸ There is a concern that the administration of RT to breast tissue results in a greater radiation dose to the lungs in patients with PE than in those without this condition because of the concavity of the chest wall in the former, leading to a greater frequency of pulmonary complications. Several recent studies involving dosimetric analysis of DVHs of RT to breast tissue in patients with PE revealed that IMRT delivers a smaller ipsilateral lung dose than 3D-CRT.^{9–11,29} However, no studies have reported follow-up data on the development of RILD after RT. In the present study, we examined the relationship of three representative chest wall depression indices (HI, FSI, and MDI) in patients with and without PE to the development of RILD. We identified no correlations between HI, FSI, and MDI and increase in density on CT images, indicating that PE is not a risk factor for RILD.

However, similar to previous reports, we did identify strong correlations between both low and high ipsilateral lung doses (V5–V30) as determined from DVHs and RILD, and found that the higher the radiation dose, the higher the incidence of RILD. In addition, we found strong correlations between ipsilateral lung dose and all assessed chest wall depression indices (HI, FSI and MDI), indicating that as depression increases, the ipsilateral lung dose increases. In summary, we found that, although the ipsilateral lung dose is higher in individuals with PE, curiously,

even when administered high ipsilateral lung doses, such individuals are less likely to develop RILD than individuals without this condition. Although we do not have a clear explanation for this, anatomical differences may be involved. It is possible that in individuals with PE the lung extending toward the abdomen is more peripheral than the irradiated lung in individuals without PE, making it less likely for RILD to develop, even with high ipsilateral lung doses. Comparison of individuals with and without PE but with similar DVHs may reveal that the distance between the radiation field and central bronchus area is greater in those with PE than in those without PE. Patients with lung cancer are reportedly more likely to develop bronchial stricture and radiation pneumonitis after stereotactic body radiation therapy when RT is applied to the central as opposed to peripheral regions of the lung.^{30,31}

As a retrospective study, our analysis has the following limitation: the timing of CT was irregular.

Our analysis revealed that PE is not correlated with risk of RILD, even with high ipsilateral lung doses. To explain this finding we intend to further investigate relevant patients and analyze the relationship between the radiation field and central bronchi.

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Disclosure

No authors report any conflict of interest.

References

- Julien JP, Bijker N, Fentiman IS *et al.* Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: First results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet* 2000; **355**: 528–33.
- Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002; **347**: 567–75.
- Clarke M, Collins R, Darby S *et al.* Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005; **366**: 2087–106.
- Darby S, McGale P, Correa C *et al.* Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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.
- Teshima T, Numasaki H, Nishio M *et al.* Japanese Society for Therapeutic Radiology and Oncology Database Committee. Japanese structure survey of radiation oncology in 2009 based on institutional stratification of the Patterns of Care Study. *J Radiat Res* 2012; **53**: 710–21.
- Lind PA, Wennberg B, Gagliardi G, Fornander T. Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose. *Breast Cancer Res Treat* 2001; **68**: 199–210.
- Lind PA, Marks LB, Hardenbergh PH *et al.* Technical factors associated with radiation pneumonitis after local +/- regional radiation therapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2002; **52**: 137–43.
- Teh AY, Park EJ, Shen L, Chung HT. Three-dimensional volumetric analysis of irradiated lung with adjuvant breast irradiation. *Int J Radiat Oncol Biol Phys* 2009; **75**: 1309–15.
- Teh BS, Lu HH, Sobremonte S *et al.* The potential use of intensity modulated radiotherapy (IMRT) in women with pectus excavatum desiring breast-conserving therapy. *Breast J* 2001; **7**: 233–9.
- Uhl M, Sterzing F, Hahl G *et al.* Breast cancer and funnel chest. Comparing helical tomotherapy and three-dimensional conformal radiotherapy with regard to the shape of pectus excavatum. *Strahlenther Onkol* 2012; **188**: 127–35.
- Perni S, Kim SK, Chin C, Pfister NT, Tiwari A, Horowitz DP. Radiation therapy for right-sided breast cancer in a patient with pectus excavatum: A comparison of treatment techniques. *Pract Radiat Oncol* 2016; **6**: 383–7.
- Bollet MA, Campana F, Kirova YM *et al.* Breast radiotherapy in women with pectus excavatum (funnel chest): Is the lateral decubitus technique an answer? A dosimetric study. *Br J Radiol* 2006; **79**: 785–90.
- Haller JA Jr, Kramer SS, Lietman SA. Use of CT scans in selection of patients for pectus excavatum surgery: A preliminary report. *J Pediatr Surg* 1987; **22**: 904–6.
- Kilda A, Basevicius A, Barauskas V, Lukosevicius S, Ragaisis D. Radiological assessment of children with pectus excavatum. *Indian J Pediatr* 2007; **74**: 143–7.
- Backer OG, Brunner S, Larsen V. Radiologic evaluation of funnel chest. *Acta Radiol* 1961; **55**: 249–56.
- Ohno K, Morotomi Y, Nakahira M *et al.* Indications for surgical repair of funnel chest based on indices of chest wall deformity and psychological state. *Surg Today* 2003; **33**: 662–5.
- Monden Y, Taniki T, Uyama T, Nakahara K, Fujimoto Y. Morphological analysis of thoracic cage in funnel chest and

- postoperative evaluation. *Nihon Kyobu Geka Gakkai Zasshi* 1986; **34**: 1121–5.
- 18 Radiation Therapy Oncology Group. *RTOG 1005 Protocol*. version date 07/31/2014 Available from URL: <https://www.rtog.org/clinicaltrials/protocolltable/studydetails.aspx?study=10052014>
 - 19 Nishioka A, Ogawa Y, Hamada N, Terashima M, Inomata T, Yoshida S. Analysis of radiation pneumonitis and radiation-induced lung fibrosis in breast cancer patients after breast conservation treatment. *Oncol Rep* 1999; **6**: 513–7.
 - 20 Choi YW, Munden RF, Erasmus JJ et al. Effects of radiation therapy on the lung: Radiologic appearances and differential diagnosis. *Radiographics* 2004; **24**: 985–98.
 - 21 Lingos TI, Recht A, Vicini F, Abner A, Silver B, Harris JR. Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. *Int J Radiat Oncol Biol Phys* 1991; **21**: 355–60.
 - 22 Marks LB, Yu X, Vujaskovic Z, Small W Jr, Folz R, Anscher MS. Radiation-induced lung injury. *Semin Radiat Oncol* 2003; **13**: 333–45.
 - 23 Minor GI, Yashar CM, Spanos WJ Jr et al. The relationship of radiation pneumonitis to treated lung volume in breast conservation therapy. *Breast J* 2006; **12**: 48–52.
 - 24 Krengli M, Sacco M, Loi G et al. Pulmonary changes after radiotherapy for conservative treatment of breast cancer: A prospective study. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1460–7.
 - 25 Graham MV, Purdy JA, Emami B et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999; **45**: 323–9.
 - 26 Allen AM, Czerminska M, Jänne PA et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006; **65**: 640–5.
 - 27 Sarwar ZU, DeFlorio R, O'Connor SC. Pectus excavatum: Current imaging techniques and opportunities for dose reduction. *Semin Ultrasound CT MR* 2014; **35**: 374–81.
 - 28 Stahl JM, Hong JC, Lester-Coll NH et al. Chest wall deformity in the radiation oncology clinic. *Anticancer Res* 2016; **36**: 5295–300.
 - 29 Cendales R, Vasquez J, Arbelaez JC et al. Intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) in a patient with left breast cancer and pectus excavatum. *Clin Transl Oncol* 2012; **14**: 747–54.
 - 30 Timmerman R, McGarry R, Yiannoutsos C et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; **24**: 4833–9.
 - 31 Song SY, Choi W, Shin SS et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. *Lung Cancer* 2009; **66**: 89–93.