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Pneumonitis and fibrosis after breast cancer radiotherapy: occurrence and treatment-related predictors.

Abstract

Background:

Radiation pneumonitis (RP) and radiation fibrosis (RF) are common side effects after breast cancer (BC) radiotherapy (RT). However, there is a great variation in the frequency of RP and RF. This study presents the occurrence of- and the treatment-related predictors for RP and RF. Further, physician- and patient-reported pulmonary symptoms during the first year after postoperative RT for BC are demonstrated.

Materials and methods:

From 2007 to 2008, 250 BC patients referred for postoperative RT were included in a prospective cohort study and followed during the first year after RT. High-resolution computed tomography of the lungs and symptom registration were performed before RT and 3, 6, and 12 months after RT. Patient-reported symptoms were registered by standard quality of life questionnaires. Logistic regression analyses were applied to estimate treatment-related predictors for radiological RP (rRP), clinical RP (cRP), radiological RF (rRF) and clinical RF (cRF).

Results:

The occurrence of rRP and cRP at 3 months was 78% and 19%, while 12 months after RT rRF and cRF were 89% and 16%, respectively; all reported as grade 1. In multivariable analyses mastectomy

predicted cRP at 3 months (OR=2.48, p=0.03) and cRF at 6 months, ipsilateral lung volume receiving 20 Gray or more (V20), V30, and mean lung dose (MLD) predicted rRP at 6 months (OR=1.06, p=0.0003; OR=1.10, p=0.001; and OR=1.03, p=0.01, respectively). Endocrine treatment predicted cRF at 12 months (OR=2.48, p=0.02). Physicians reported significantly more dyspnea at 3 months (p=0.003) and patients reported “a little dyspnea” more at 3 and 12 months compared to baseline (p=0.007).

Conclusion:

RP and RF are prevalent in the first year after BC radiation. Mastectomy predicted cRP at 3 months. V20, V30, D25 and MLD predicted rRP at 6 months, and endocrine treatment predicted cRF at 12 months. Patients and physicians reported dyspnea differently.

Key words: radiation pneumonitis fibrosis breast cancer

Background

Breast cancer (BC) is the most common cancer among women in Norway, with 3568 new cases reported in 2018.The combination of increased survival with a current five-year survival rate of 90.4% and a close to 10% increase in incidence during the last decade have resulted in a steep rise in long-time BC survivors [1]. Radiation therapy (RT) prevents local recurrence, reduces BC-related mortality, and improves overall survival [2,3]. However, RT may induce lung tissue damage ranging from symptom-free radiological changes to respiratory failure [4,5]. Lung toxicity after RT may present as radiation pneumonitis (RP) or radiation fibrosis (RF) [6,7]. Usually, RP appears within 1–3 months after RT. RF develops 6–12 months after RT and may progress for up to 2 years before stability occurs.

The frequencies of RP and RF are reported with wide heterogeneity in the literature. In a meta-analysis, low-grade RP ranged from 22% to 62%, with a median overall frequency of 42% [8]. Much of the current data on RP and RF are based mainly on retrospective studies using older RT techniques [4,9,10].

The large variation in the frequencies of RP and RF may be explained using different diagnostic tools such as chest radiography, CT, and high-resolution CT (HRCT). Furthermore, the lack of standardized international RT guidelines concerning the borders of the clinical target volume (CTV) and the inclusion of the internal mammary nodes [11,12], may influence the variability in RP and RF development.

Locoregional RT (compared to local RT), increased mean lung dose (MLD), and ipsilateral lung volume receiving ≥ 20 Gray (Gy) (V20) >30% have been identified as risk factors for RP and RF [8,13]. Patient-specific factors such as age, comorbidity, body mass index (BMI), and treatment-related factors such as chemotherapy, endocrine therapy, and trastuzumab have also been associated

with lung toxicity [9,14-17]. Smoking has been reported to be a protective factor against RP, probably due to suppression of local inflammatory reactions [18,19].

Clinical RP and RF defined as radiological RP or RF in combination with symptoms are reported heterogeneously [8] and may reflect the use of different radiological diagnostic techniques and different classification systems such as Common Terminology Criteria for Adverse Events (CTCAE) and Radiation Therapy Oncology Group (RTOG) [5]. Physicians may both underestimate and miss symptoms reported by patients, leading to under-management of symptoms and unnecessary suffering [20]. Using Patient Reported Outcome Measures (PROMs) in the clinical setting may enhance communication between patient and physician and thereby improve care and clinical outcomes [21].

The primary aim of the present study was to demonstrate the occurrence of radiological and clinical RP and RF after conventional BC RT. Secondary aims were to examine the treatment-related predictors for- and the association between RP and RF. Finally, we report the frequency of pulmonary symptoms reported by physicians and patients during one year after RT.

Materials and methods

Study population

BC patients referred for postoperative adjuvant breast RT were consecutively invited to this single institution, < prospective longitudinal cohort study. Exclusion criteria were metastatic disease and inability to provide confirmed consent or to understand the Norwegian language.

Patients were provided oral and written study information during their first visit to the department of oncology, and they gave their informed consent before the start of RT. The study was approved by the VC, FEV1, FVC and DLCO

Assessments

Assessments were conducted through extended outpatient follow-ups that took place at the hospital before RT (baseline) and at 3, 6, and 12 months after baseline. At baseline, clinical and treatment characteristics such as age, comorbidity, BMI, chemotherapy, trastuzumab, endocrine therapy, and type of surgery were registered. At each assessment, the patients underwent clinical examination of the lungs, and dyspnea and coughing, which reflected the most common symptoms of RP [4,5] were registered by an oncologist using CTCAE v.3.0. The physicians could at the same assessments register if patients had other causes of dyspnea and coughing, such as infections or other comorbidities.

Radiological lung examination was performed by HRCT at baseline and after 3, 6, and 12 months. All grading of RP and RF was evaluated by one and the same radiologist. Radiological RP (rRP) were defined as lung consolidations and ground-glass opacities; and radiological RF (rRF) as reticular marketing, interlobular septal lines, fibrotic changes, or presence of pleura thickness in the radiated field [6]. Quantification of fibrosis in the CT-scans was performed according to CTCAE v3.0 where grade 1 indicates <25% of the total lung volume is fibrotic. cRP and cRF were defined as the combination of rRP or rRF and symptoms of dyspnea and/or coughing according to CTCAE v 3.0.

Estimated lung dose volumes V20, V30, MLD, and dose to 25% of ipsilateral lung (D25) were retrieved from the Oncentra dose planning system. PROMs were assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC

QLQ-C30) version 3.0 [22]. Severity of symptoms was rated on a four-point ordinal scale from 1 (not at all) to 4 (very much).

Treatment

RT was planned using the CT 3D image-based dose planning system, Oncentra MasterPlan®, ONCENTRA, Nucletron B.V. Local RT was delivered to the breast/chest wall (50 Gy in 2 Gy/fraction, 5 days a week) with two 6-MV photon tangential fields, frequently supplemented by low-weighted field segments to achieve optimal dose homogeneity. Target were delineated according to national guidelines (www.nbcg.no). The posterior border of the CTV after mastectomy was the anterior border of the costae, and after breast conserving surgery (BCS) the posterior border was the ventral part of the major pectoralis muscle. Patients with verified pathological axillary lymph node metastases (pN+) also received 46 Gy to regional lymph nodes in the periclavicular region. No patients received RT to internal mammary nodes. In patients receiving chemotherapy, treatment ended 3–4 weeks before enrollment in the study.

Statistical analysis

The variables rRP, rRF, cRP, and cRF were examined through descriptive statistics for each timepoint and the association between rRP at 3 months and rRF at 12 months were assessed using Fisher's exact test.

Logistic regression analysis was used for outcome variables rRP and cRP at 3 months, rRP at 6 months, and rRF and cRF at 6 and 12 months after start of RT. The number of cases with cRP at 6 months were too few for logistic regression analysis. The treatment-related predictors mastectomy, chemotherapy, endocrine therapy, trastuzumab, locoregional RT, V20, V30, MLD, and D25, as well as the personal variables age, BMI, comorbidity, and current smoking were first analyzed one-by-one in a univariate logistic regression model. Treatment-related predictors were analyzed separately as most of them represent various expressions of lung dose and/or lung volume. In all multivariable

models, analyses were adjusted for the personal variables age, BMI, comorbidity, and smoking. In the literature these factors are associated to RP and RF and were a priori assumed to influence the effects of the treatment-related predictors. For simplicity, only significant predictors are presented in Table 3, while complete models (with all variables) are available in the supplementary materials.

Physician- and patient-reported score changes from baseline at 3,6 and 12 months, and the difference between physician-reported dyspnea "grade 1" and patient-reported dyspnea "quite a bit/very much" were analyzed using McNemar's test. All tests were two-sided, and the significance level was set to ≤ 0.05.

Data were analyzed with the SPSS software version 25 (IBM CORP, Armonk. NY, USA, 2017).

Results

From February 2007 to October 2008, 250 patients were consecutively included in this prospective study. Compliance to follow-up is shown in Figure 1. Details on missing data are presented in the supplementary materials. Endocrine therapy with tamoxifen or aromatase inhibitors was given concomitant with RT in 89% of cases, while 11% started immediately after RT. The clinical and treatment background information, including dosimetric values, is described in Table 1 for the total sample. In patients with locoregional RT mean V30 and V20 were 22% and 29%, respectively, compared to 13% and 15%, in patients with local RT.

The occurrence of radiological and clinical RP and RF.

The highest frequency of rRP and rRF was observed at 3 months and 12 months, respectively. Of the 179 patients with rRP at 3 months, 156 (87%) developed rRF at 12 months. The association between rRP at 3 months and rRF at 12 months was statistically significant ($p = 0.003$). Of the 200 patients with rRF at 12 months, 36 (18%) had no rRP at 3 months. The highest occurrence of cRP

was observed 3 months after RT (19%), and the highest cRF was after 12 months (17%). All symptoms were registered as grade 1 except for three patients with grade 2 at 3, 6 and 12 months (Table 2). Grade 1 represents dyspnea with moderate exertion and coughing without medical intervention.

The predictors of radiological and clinical RP and RF

Based on univariate logistic regression analysis, smoking was significantly associated with less rRP at 3 months. Mastectomy predicted cRP at 3 months and cRF 6 months and remained a significant independent predictor after adjusting for the personal variables age, BMI, comorbidity, and smoking in multivariable logistic regression analysis (Table 3). The RT variables V20, V30, and MLD significantly predicted **r**RP at 6 months in both univariable and multivariable analysis. V30 emerged as the strongest independent predictor for rRP at 6 months (OR= 1.10, p = 0.001).

None of the treatment-related variables were able to predict rRF at 12 months, but endocrine treatment significantly predicted cRF in both univariable analysis and after adjustments for personal variables in the multivariable analysis. In subgroup analyses, Tamoxifen emerged as an independent predictor for cRF at 12 months, but aromatase inhibitors did not. Among the 114 patients using Tamoxifen, 70% had developed rRF at 12 months, and 20% had developed cRF at 12 months**.** Among the 23 aromatase inhibitor users, 6% had rRF and 1% had cRF at 12 months.

Physician- and patient-reported symptoms of pneumonitis or fibrosis

The physician-registered symptoms were modest at all timepoints, and the frequency is outlined in Table 4. Physicians reported significantly more frequent dyspnea at 3 months (p = 0.003) compared to baseline, but no significant changes were seen at 6 months or 12 months, nor any significant changes in coughing at any timepoint. Patients reported significantly more frequent “a little” dyspnea at 3 months (p=0.007) and 12 months (p=0.03) compared to baseline, but not at 6 months (p=0.06).

The comparison of patient- and physician-reported dyspnea is illustrated in Figure 2. Patients reported significant more frequent “a little” dyspnea than physicians (grade 1) at all timepoints, but when comparing with patients’ “quite a bit/very much”, no significant differences were seen, except for at 3 months after RT, were physicians reported significant more frequent dyspnea than patients (p=0.01).

Discussion

This large prospective cohort study reports that rRP and rRF are quite common the first year following conventional RT for BC. cRP and cRF are less frequent, and most patients have minor symptoms. Radiological RP at 3 months after RT was found in 78% of our patients, a frequency similar to another prospective study diagnosing pulmonary changes by HRCT at the same timepoint after RT [16], while an older review reported rRP in 27–40% of patients [10]. This large variability could be attributed to the use of different diagnostic tools. Studies using conventional chest x-rays in general report lower incidence of rRP than do those using HRCT[23]. Another possible explanation might be that retrospective studies underestimate the incidence of rRP due to lack of systematic data collection with the subsequent risk of introducing bias [9,24]. The use of different evaluation systems such as CTCAE and RTOG may reflect some of the substantially different occurrences of rRP and rRF [14,25-27].

Twelve months after RT rRF was identified in 89% of patients, which is similar to findings from a study of 52 BC patients demonstrating fibrotic changes by chest CT in 90% (27). Studies on rRF after BC RT are mostly older and demonstrate lower frequency of rRF [4,28]. In a study evaluating 328 BC paients, rRF was found in only 30% one year after RT. Compared to our study, they had no baseline measures and ordinary CT was used, which may explain the lower frequency of rRF [26]. The observed rP in 6% of our patients before RT could be associated with comorbidity or chemotherapy [6,7,29]. As rRP grade 1 represents that 1-24% of total lung is fibrotic there may be a

certain variation of the actual extent of RF. The diagnosis is though not very specific which may explain why patients with rRF display a variety in symptom pattern.

Our prospective study demonstrated a strong significant association between rRP at 3 months and rRF at 12 months, which replicates findings in another study (30), and supports the hypothesis that rRF represents an end stage of rRP [5]. However, 18% of our patients with rRF at 12 months did not have rRP at 3 months, which supports the evidence that fibrosis may develop due to chronic pulmonary damage and thus present without being preceded by rRP [4]. One possible cause may be the use of tamoxifen, which has been shown to be an independent risk factor for lung fibrosis [27,29].

Clinical RP and RF were less prevalent in the present study. We identified cRP grade 1 in 19% of cases at 3 months and cRF in 17% at 12 months. Our findings are similar to a multicenter study reporting an overall cRP frequency of 14%, [8]. Lind reported a higher incidence of moderate and serious pulmonary side effects among locoregional radiated patients [30]. However, in Lind's study, 46% had internal mammary lymph node RT compared to no patients in our study, resulting in a higher volume of lung exposed to radiation. Diagnosing cRP and cRF may be challenging due to comorbidities such as lung or heart disease or infections in the upper airways or lungs. Dyspnea and coughing registered at baseline may be associated to comorbidity, side effects of chemotherapy and/or smoking. In our study, 22% of patients with rRP at 3 months had comorbidities. However, we did not find comorbidity to be a significant predictor for rRP. Most patients had cRP and cRF grade 1, indicating that few patients had symptoms affecting their daily living. Other symptoms of cRP such as low-grade fever, chest pain and hemoptysis were not registered, and we may thus underestimate the number of cRP. Though assessment of cRP and cRF was standardized according to CTCAE, the threshold for diagnosing cRP and cRF may vary among physicians. Studies have shown that healthcare providers underestimate cancer treatment side effects and the severity of symptoms [20].

Mastectomy emerged as a significant predictor for cRP at 3 months and cRF 6 months. After mastectomy, 74% of patients received locoregional RT, compared to 17% who received breast-conserving surgery. Mastectomy as a predictor for cRP and cRF may be associated with the thin thoracic wall after surgery, which results in an increased dosage into the lungs, especially with locoregional RT after BCS. The evidence of mastectomy as a predictor for cRP and cRF is sparse. Huang reported low BMI as a predictive factor for RF after postmastectomy RT, possibly associated to more electron beam penetration through the thin chests of slim patients, resulting in an increased volume of the lung being irradiated [27].

In our study, V20, V30, D25, and MLD were all significant predictors for RP. Our results are similar to another prospective study with 116 BC patients [25]. We found the OR for V20 to be 1.06, giving a 6% increased risk of RP with every percent increase in V20. Similarly, we found an OR of 1.10 for V30, giving a 10% increased risk of RP with every percent increase in V30. D25 emerged as a statistically significant predictor for RP after adjustments in the multivariable analyses. With an OR at 1.03, the odds of developing RP increase by 3% for every Gy increase in D25.

MLD was positively associated with the risk of developing RP and RF. With an OR of 1.12, the odds of developing RP increase by 12% for every Gy increase in MLD. In our study, MLD was 11.2 Gy in patients with RP at 6 months after RT. This dosage is above the MLD threshold for ipsilateral lung > 7 Gy, which has been identified as a risk factor for cRP [31]. Defining an exact threshold for MLD is challenging considering that personal and treatment-related factors associated with RP and RF, such as smoking and use of Tamoxifen, may vary among BC patients. Nevertheless, the authors of a meta-analysis recommend MLD <12-15 Gy in BC patients to avoid serious lung toxicity [8].

Minimizing dose to the lung using 3D dose-planning systems may be challenging. Reducing CTV may be necessary, but the risk of side effects must be balanced against administering an adequate

dosage to the target (i.e., the breast, thoracic wall, and regional lymph nodes). From that perspective, new RT techniques such as Volume Modulated Arc Therapy (VMAT), [32,33], hybrid VMAT [34], Deep inspiration breath-holding technique [35] and Proton beam therapy may be preferred. [36]. Furthermore, hypofractionated RT (40.5 Gy in 15 fractions) has documented lower incidence of rRP than conventional treatment [37] and is now the recommended fractionation schedule for all BC patients in Norway.

Smoking has been found to be a protective factor for developing rRP at 3 months, and our data on this aspect seem to be in line with others [18,38]. In our study, 19% of the patients were smokers. Although smokers have a lower occurrence of rRP, they are at high risk of developing lung cancer, especially if they continue smoking after RT [39].

Tamoxifen emerged as a significant independent predictor for cRF at 12 months. Tamoxifen associated to rRF, mainly grade 1 and without symptoms, is documented in other studies [26,27,29]. We found no association between aromatase inhibitors and rRF, similarly to Varga et al. [26]. In Norway, the treatment guidelines were in 2013 changed from five to 10 years tamoxifen use in premenopausal BC patients. Whether this practice has increased the number of patients with lung fibrosis after BC RT is unknown. Likewise, whether concomitant use of tamoxifen results in more rRF than sequential is not very well documented [28].

Physicians reported significantly more frequent dyspnea at 3 months but not at 6 and 12 months compared to baseline. This may be due to the fact that RP is a clinical diagnosis whereas RF occurring 6-12 months after RT is mainly radiological changes with minor symptoms.

Patients reported significantly more frequent “a little” dyspnea than physicians (grade 1) at all timepoints, but when comparing with reports of “quite a bit/very much”, no significant differences were seen between physicians and patients. Physicians may have underreported symptom severity, as demonstrated in a multicenter study of cancer patients [20]. The discrepancy may also be

attributed to different scoring systems used by patients (EORTC QLQ-C30) versus physicians (CTCAE). Poor correlation between physician- and patient-reported toxicity is well known [21]. Patients may also report fewer symptoms over time due to the phenomenon of "response shift," where patients gradually adapt to health changes [40]. Using PROMs in a clinical setting may improve accuracy in symptom detection.

The present study is one of the largest ongoing, prospective, and population-based studies including patients referred for BC RT, and the results should therefore have a relatively high external validity. Our findings confirm the association between rRP and rRF, and the study is one of few new studies to investigate the development of rRF after BC RT. The patients have been under continuous follow-up, and our results regarding rRP and rRF are in accordance with what to expect after conventional RT for BC. A long-term (10-year) follow-up study of this patient cohort is ongoing.

Some limitations are present. Few patients had severe symptoms, making the identification of predictive factors for moderate and serious symptoms difficult. Several physicians assessed the patients at the clinical visits, and interpersonal variations may influence the degree of symptom registration.

Conclusions

This prospective study demonstrates a high prevalence of rRP and rRF in the first year after BC RT and cRP and cRF were most frequent at 3 and 12 months, respectively. V20, V30, MLD and D25 were significant predictors for rRP at 6 months. We found a strong significant association between rRP at 3 months and rRF at 12 months. Our findings support the necessity of complying with recommended dose planning thresholds. Mastectomy emerged as a significant predictor for cRP 3

months and cRF 6 months, which could be related to a large lung volume irradiated. Tamoxifen emerged as a significant predictor of cRF, and sequential endocrine treatment may be an alternative for patients at high risk for lung toxicity.

Physicians and patients agreed on symptom pattern of higher severity, but low severity symptoms were to a smaller degree registered by physicians. Including PROMS into the BC clinical follow-up programs may enhance the precision of the toxicity reporting. Long-term prospective studies after modern RT are warranted, especially to identify predictors for moderate and severe long-term pulmonary effects.

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Tables

Table 1. Patient and treatment characteristics

	n (%)	Mean (SD)
Age (year)		58.1 (9.9)
Age, range (year)		28 - 89
BMI		26.1 (4.5)
BMI, range		16.7 - 44.8
Comorbidity	59 (24)	
- Cardiovascular disease	35 (14)	
- Lung disease	10 (4)	
- Other (kidney, rheumatoid arthritis diabetes, depression)	14 (6)	
Smoking	47 (19)	
pT1	165 (66)	
pT2	49 (20)	
pT3/4	16 (6)	
Tis	20 (8)	
Axillary node positive	73 (29)	
Grade 1	51 (21)	
Grade 2	107 (44)	
Grade 3	83 (34)	
ER positive	191 (83)	
PR positive	133 (58)	
HER-2 positive	49 (22)	
IDC / ILC	216 (86)	
DCIS	34 (14)	
Chemotherapy	103 (41)	
FEC 60 x 6	57 (23)	
FEC 100 x 6	27 (11)	
FEC 60 x 6 + Docetaxel x 4	19 (8)	
Endocrine therapy	***137 (56)***	
Tamoxifen	114 (46)	

Aromataseinhibitor	23 (9)
Tratuzumab[1]	34 (146)
Surgery	
Mastectomy	69 (28)
Breast conserving surgery	181 (72)
Radiation therapy	
Local RT	168 (67)
Locoregional RT	82 (33)
RT to axilla	38 (15)
Boost	28 (11)
Dosemetric values	
V20 (%)	9.6 ± 8.5
V30 (%)	15.7 ± 6.4
Mean Lung Dose (MLD (Gy)	10.7 ±8.5
D25 (Gy)	12.6 ± 11.1
Local RT (Gy)	8.1 ± 2.44
Loco-regional RT (Gy)	14.0 ± 2.33

T= tumor size according to AJCC staging 7th edition, ER=estrogen receptor>=10 %, PR progesterone receptor, HER-2=human epidermal growth factor receptor by FISH, IDC= invasive ductal carcinoma, ILC= invasive lobular carcinoma, DCIS=ductal carcinoma in situ. FEC 60= 5-Fu 600mg/m2, Epirubicin 60mg/m2 and Cyclofosfamide 600mg/m2. FEC 100= Epirubicin100mg/m2. EC = Epirubicin 60mg/m2 Cyclofosfamide 600mg/m2. Docetaxel = Docetaxel 100mg/m2. Tratuzumab[1]= 4 doses trastuzumab given concomitant with docetaxel and thereafter for totally one year. Local = the whole breast. Loco-regional= the whole breast or the chestwall and fossa supraclav/axillaregion

Table 2. Radiological and symptomatic radiation pneumonitis and fibrosis reported by CTCAE.

	Before RT n (%)		3 months n (%)	6 months n (%)	12 months n (%)
rP	3 (1)	rRP	179 (78)	52 (23)	4 (2)
crP	1 (0.4)	cRP	42 (19)	9 (4)	0
rF	15 (6)	rRF	42 (18)	189 (84)	200 (89)
crF	3 (1)	cRF	11 (5)	35 (16)	38 (17)

rP =radiological pneumonitis. crP = clinical rP (rP and symptoms). rF = radiological fibrosis. crF = clinical rF . rRP= radiological radiation pneumonitis. cRP = clinical radiation pneumonitis. rRF = radiological radiation fibrosis. cRF = clinical radiation fibrosis. All symptoms were reported as grade 1 except for two grade 2 at baseline (one dyspnoea and one coughing), and one grade 2 (coughing) at 3, 6 and 12 months, respectively.

Table 3. Predictors for pneumonitis and fibrosis by univariate and multivariable logistic regression analysis.

	Univariable			*Multivariable*		
	OR	CI	P	OR	CI	P
rRP 3 months						
Smoking	0.29	0.10-0.64	0.01	0.28	1.31-2.34	0.001
cRP 3 months						
Mastectomy	2.50	1.25-5.00	0.01	2.48	1.15-5.34	0.02
rRP 6 months						
V20	1.05	1.01-1.09	0.01	1.06	1.02-1.10	0.003
V30	1.08	1.03-1.13	0.003	1.10	1.04-1.16	0.001
MLD	1.10	1.01-1.20	0.03	1.12	1.03-1.23	0.01
D25	1.03	0.99-1.05	0.06	1.03	1.00-1.06	0.03
Age	1.03	0.99-1.06	0.08	1.03	0.99-1.06	0.12
BMI	1.06	0.99-1.13	0.11	1.05	0.98-1.13	0.19
cRF 6 months						
Smoking	0.50	0.22-1.14	0.10	0.50	0.21-1.16	0.10
Mastectomy	2.43	1.13-5.46	0.02	2.73	1.14-6.55	0.03
cRF 12 months						
Endocrine treatment	2.32	1.09-4.96	0.03	2.31	1.07-4.97	0.03
Tamoxifen	1.87	1.04-3.40	0.04	2.12	1.13-3.97	0.02
Comorbidity	1.78	0.82-3.87	0.14	0.81	0.34-1.89	0.62

RP=radiation pneumonitis, cRF =symptomatic radiation pneumonitis, RF=radiation fibrosis, cRF= symptomatic radiation fibrosis, OR= odds ratio, P=p-value, CI=confidence interval, V20=percent of ipsilateral lung given 20 Gy or more, V30=percent of ipsilateral lung given 30 Gy or more, MLD=mean lung dose.

Table 4. Physician-reported dyspnea and coughing by CTCAE

Symptom	*Baseline (n=243) n (%)*	*3 months (n=218) n (%)*	*6 months (n=223) n (%)*	*12 months (n=225) n (%)*
Dyspnea	21 (9)	36 (17)*	23 (11)	26 (12)*
Coughing	27 (11)	30 (14)	21 (9)	22 (10)
Dyspnea and coughing	15 (6)	15 (7)	9 (4)	6 (3)

CTCAE = Common Terminology Criteria for Adverse Events. All symptoms reported as grade 1 except one dyspnoea grade 2 at baseline and one coughing grade 2 at baseline, one at 6 months and one at 3 and 12 months respectively.
**Significant more frequent reported dyspnoea compared to baseline*

Figure 1.

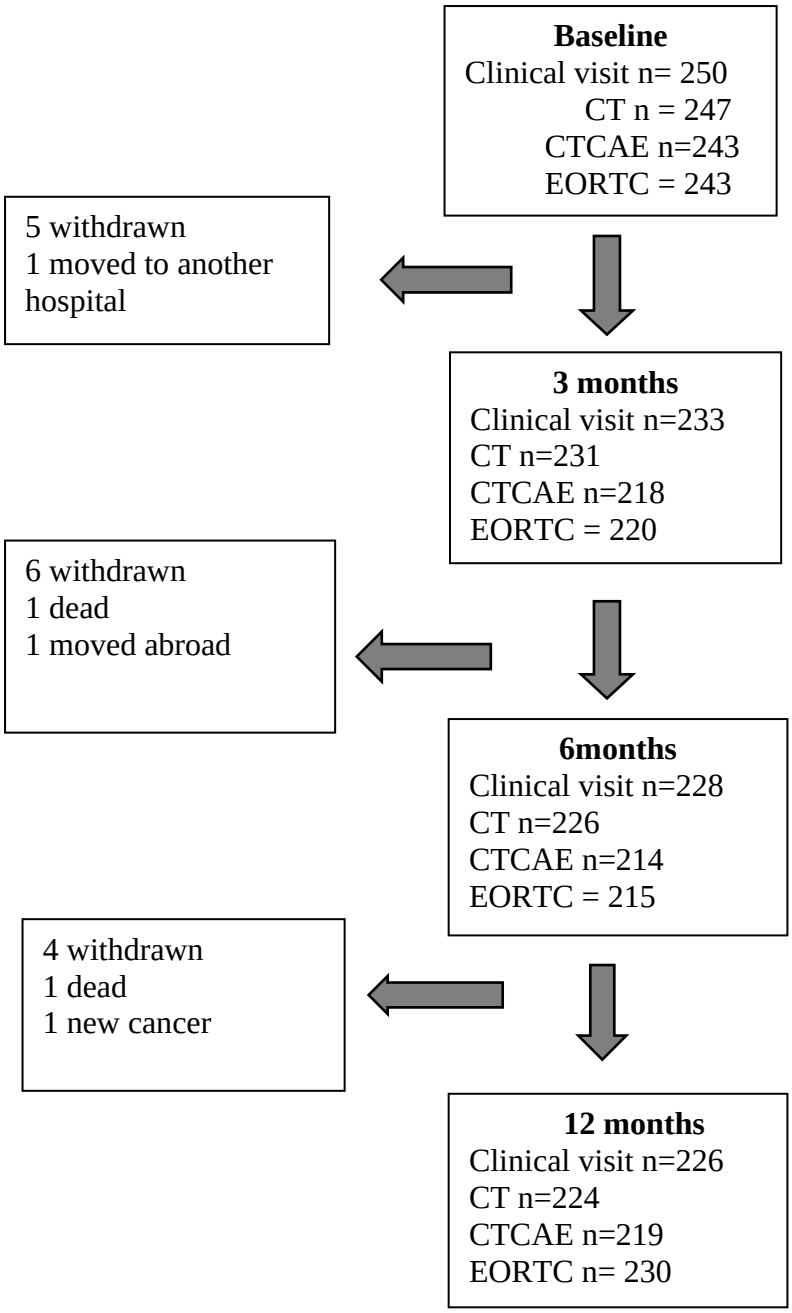
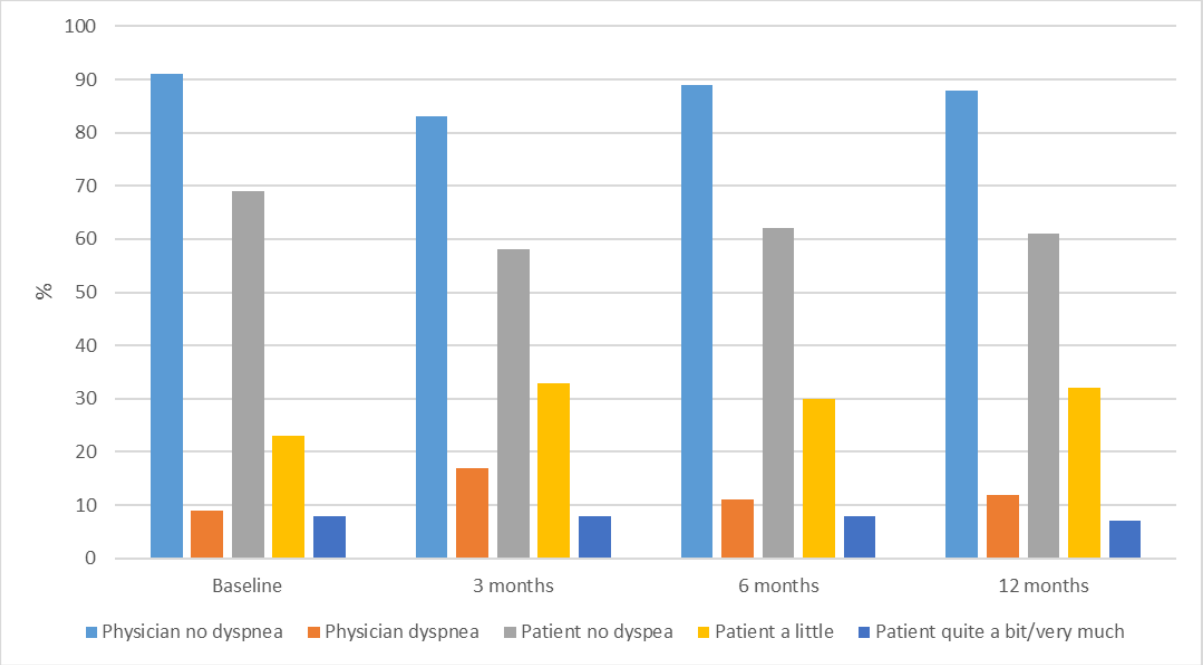

Baseline
Clinical visit n= 250
CT n = 247
CTCAE n=243
EORTC = 243
5 withdrawn
1 moved to another hospital
3 months
Clinical visit n=233
CT n=231
CTCAE n=218
EORTC = 220
6 withdrawn
1 dead
1 moved abroad
6months
Clinical visit n=228
CT n=226
CTCAE n=214
EORTC = 215
4 withdrawn
1 dead
1 new cancer
12 months
Clinical visit n=226
CT n=224
CTCAE n=219
EORTC n= 230

Figure 2.



Legends to figures

Figur 1. Consort diagram.

Clinical visit by physician, CT, CTCAE and EORTC registration at baseline and at 3, 6 and 12 months after radiotherapy. Excluded patients at the right.

Figure 2. Physician- and patient-reported dyspnea during the first year after radiotherapy.

Columns represent the number of patients. Physician-reported (green column) by CTCAE and patient-reported by EORTC as a little (blue column) and quite a bit/very much (yellow column).

Supplementary Material

A1. ***Missing clinical visits, CT, CTCAE or EORTC registrations.***

Missing data	***Baseline***	***3 months***	***6 months***	***12 months***
Patients' choice: reason not stated	3	5	2	3
Patients' choice due to long distance, disease in the family or to unwell to go	0	6	6	1
Physicians forgot to order CT	0	2	1	1
Patients forgot CT	0	0	1	1
Physicians forgot EORTC	7	15	14	7
No EORTC data from patients	7	24	21	0

A2. Registration of dyspnea by patients (EORTC)

Dyspnea	**Baseline**	**3 months**	**6 months**	**12 months**
n(%)	243	220	215	230
Not at all	167 (68.7)	126 (57.3)	133 (61.9)	138 (60.0)
A little	55 (22.7)	74 (33.6)	64 (29.8)	77 (33.3)
Quite a bit	18 (7.4)	18 (8.2)	17 (7.9)	11 (4.8)
Very much	3 (1.2)	2 (0.9)	1 (0.4)	4 (1.7)
Missing	7 (2.8)	30 (12.0)	35 (14.0)	20 (8.0)

A3. Univariable and multivariable logistic regression

	Univariate			*Multivariable*		
	OR	***CI***	***P***	***OR***	***CI***	***P***
RP 3 months						
Smoking	0.29	0.10-0.64	0.01			
Age	1.00		0.98			
Comorbidity	0.84		0.64			
BMI	1.01		0.76			
Chemotherapy	0.99		0.99			
Endocrine therapy	1.30		0.41			
Locoregional RT	0.77		0.42			
V20	0.88		1.00			
V30	1.01		0.79			
MLD	1.02		0.74			
D25	1.00		0.84			
Mastectomy	1.40		0.36			
cRP 3 months						
Smoking	0.59		0.31			
Age	1.01		0.49			
Comorbidity	1.33		0.49			
BMI	0.95		0.25			
Chemotherapy	1.40		0.36			
Endocrine therapy	0.36		1.38			
Locoregional RT	1.12		0.59			
V20	1.02		0.43			
V30	1.03		0.34			
MLD	1.06		0.21			
D25	1.01		0.38			
Mastectomy	2.50	1.25-5.00	0.01	2.48	1.15-5.34	0.02
RP 6 months						
Smoking	0.65		0.34			
Age	1.03		0.08			
Comorbidity	1.06		0.11			
BMI	1.06		0.11			
Chemotherapy	0.95		0.78			
Endocrine therapy	1.51		0.20			
Locoregional RT	1.42		0.29			

V20	1.05	1.01-1.09	0.01	1.06	1.02-1.10	<0.01
V30	1.08	1.03-1-13	<0.01	1.10	1.04-1.16	<0.01
MLD	1.10	1.01-1.20	<0.03	1.12	1.03-1.23	0.01
D25	1.03	0.99-1.05	0.06	1.03	1.00-1.06	0.03
Mastectomy	1.14		0.75			

rRF 6 months

Smoking	0.50	0.10
Age	1.00	0.80
Comorbidity	0.68	0.33
BMI	1.01	0.75
Chemotherapy	1.08	0.84
Endocrine therapy	0.83	0.62
Locoregional RT	0.83	0.61
V20	1.01	0.80
V30	1.01	0.81
MLD	1.04	0.47
D25	1.01	0.66
Mastectomy	1.14	0.75

cRF 6 months

Smoking	0.50	0.10
Age	1.00	0.80
Comorbidity	0.67	0.33
BMI	1.01	0.75
Locoregional RT	0.83	0.61
V20	1.01	0.80
V30	1.01	0.81
MLD	1.02	0.47
D25	1.01	0.66
Mastectomy	2.49	0.02

rRF 12 Months

Smoking	0.49	0.13
Age	1.03	0.61
Comorbidity	0.70	0.42
BMI	1.01	0.93

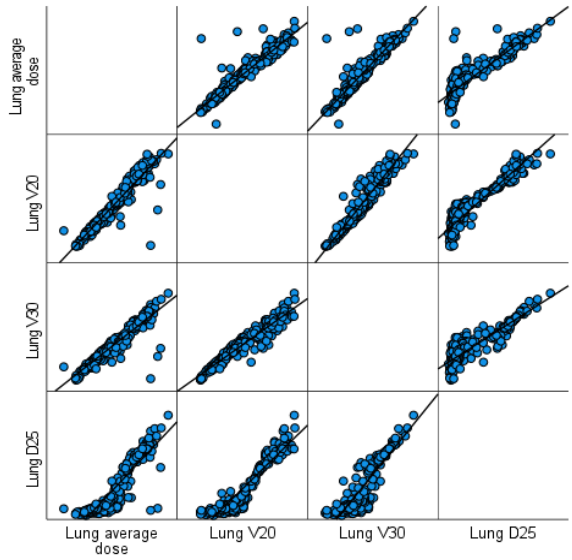
Chemotherapy	0.70		0.42			
Endocrine therapy	1.27		0.53			
Locoregional RT	0.50		0.12			
V20	1.01		0.79			
V30	1.04		0.29			
MLD	1.01		0.93			
D25	1.00		0.99			
Mastectomy	1.39		0.54			

cRF 12 months

Smoking	1.40		0.54			
Age	1.02		0.42			
Comorbidity	1.78	0.82-3.87	0.14			
BMI	1.03		0.41			
Chemotherapy	1.23		0.14			
Endocrine treatment	2.32	1.04-4.96	0.03	2.31	1.07-4.97	0.03
Locoregional RT	1.09					
V20	1.01		0.82			
V30	1.00		0.78			
MLD	1.03		0.89			
D25	1.00		0.53			
			0.81			

A4. Scatterplot V20, V30, MLD and D25

The scatterplot shows a positive correlation between V20, V30, MLD and D25.



A5. Physician- and patient-reported dyspnea

n(%)	*Physician dyspnea*	*Physician No dyspnea*	*Patient a little*	*Patient quite a bit/very much*	*Patient No dyspnea*
Baseline	21 (9)	222 (91)	55 (23)	21 (8)	167 (69)
3 months	36 (17)	182 (83)	72 (33)	20 (8)	125 (58)
6 months	23 (11)	191 (89)	63 (30)	18 (8)	133 (62)
12 months	26 (12)	194 (88)	73 (32)	15 (7)	140 (61)