Lung Restriction in Patients With Breast Cancer After Hypofractionated and Conventional Radiation Therapy

Verbanck, Sylvia; Van Parijs, Hilde; Schuermans, Daniel; Vinh-Hung, Vincent; Storme, Guy; Fontaine, Christel; De Ridder, Mark; Verellen, Dirk; Vanderhelst, Eef; Hanon, Shane

Published in:
International Journal of Radiation Oncology, Biology, Physics

DOI:
10.1016/j.ijrobp.2022.02.021

Publication date:
2022

LUNG RESTRICTION IN BREAST CANCER PATIENTS AFTER HYPOFRACTIONATED TOMOTHERAPY AND CONVENTIONAL 3D CONFORMAL RADIOTHERAPY : A 10-YEAR FOLLOW-UP

ABSTRACT

Purpose: Previous studies in breast cancer patients have shown acute radiotherapy-induced reductions of pulmonary diffusing capacity, essentially due to lung volume restriction. We aimed to assess the long-term effect of two radiotherapy regimens that differed in terms of radiation technique and dose fractionation, on lung function.

Methods and Materials: From a randomized controlled trial comparing conventional 3D conformal radiotherapy (CR) and hypofractionated tomotherapy (TT), 84 breast cancer patients (age at inclusion 54±10(SD) years) could be assessed at baseline, after 3 months, 1, 2, 3 and 10 years. Measurements included forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity (TLco).

Results: Radiotherapy-induced lung function changes over 10 years (Δ) were similar for both treatment arms, and in a patient subgroup with negligible history of respiratory disease or smoking (n=57) these averaged: ΔFVC= -13 (±9)%predicted; ΔTLco= -14 (±12)%predicted; ΔTLC= -11 (±9)%predicted; the only significant correlation was between V20 and ΔTLco (rho=-0.36;p=0.007). In this subgroup as well as in the entire patient cohort, the incurred pulmonary restriction in terms of TLC and TLco showed a greater decline at 3 months for CR vs TT. However, at 10 years, no significant difference could be detected between CR and TT (P=0.9 for TLC and P=0.2 for TLco in the entire patient cohort). Of the patients with normal TLC and TLco at baseline (i.e., above lower limits of normal), respectively 94% and 96% were still normal 10 years later.

Conclusions: In women with breast cancer, conventional 3D conformal radiotherapy and hypofractionated tomotherapy induce similar restrictive lung patterns over the course of a 10-year period, despite some treatment dependent differences in the first 3 months. The large majority of women with normal lung function at baseline maintained a normal lung function status 10 years after radiotherapy, irrespective of treatment arm.

Keywords : radiotherapy, early breast cancer, restriction, diffusing capacity, long term follow up.

INTRODUCTION

Hypofractionated radiotherapy treatment for breast cancer patients has been proposed as a good alternative for conventional radiotherapy treatment (1), and recent guidelines by the European Society for Medical Oncology (ESMO) recommend moderate hypofractionation schedules (15-16 fractions of 3 Gy/fraction) (2). With the publication of the 5-year results of the FAST-Forward trial in 2020 (3), there is a trend towards further hypofractionation in 5 fractions (4). Long-term randomized trials have shown similar cancer control and breast cosmetic outcomes between conventional and moderate hypofractionated whole breast irradiation in breast cancer patients (5-8). Toxicity to the respiratory system with either radiotherapy (RT) modality has been shown to be limited, and characterized by an acute phase of pulmonary function decline within the first months, followed by a slower deterioration over the following years, part of which can be attributed to normal ageing (9-13).

In the literature, forced vital capacity derived from spirometry (FVC) and diffusing capacity for carbon monoxide (TLco) are the most readily reported lung function variables as a reflection of lung restriction. However, to actually establish pulmonary restriction which appears to be the hallmark of RT induced changes, total lung capacity (TLC) - usually measured by bodyplethysmography - is the gold standard (14). In the present study we report FVC, TLco and TLC at 10 year follow-up, for breast cancer patients enrolled in the TomoBreast randomized clinical trial of two radiotherapy regimens that differed in terms of radiation technique and dose fractionation (15). Study randomization was between 3D-CRT with conventional fractionation (CR) and hypofractionated tomotherapy (TT). For tomotherapy, hypofractionation was in part

made possible at study onset because of the superior dose conformity and image-guidance based on daily megavoltage CT. For this patient cohort, we have previously reported changes of more specialized lung function measurements after 3 months (16) and modifications of standard lung function parameters up to 3 years (17). There was a slightly greater lung restriction after 3 months for CR versus TT, but this evolved into a similar degree of lung restriction following either radiation therapy regimen when observed over a 3- year period (17).

Over the course of this 10 year follow-up (FU) period, quality control of lung function and its interpretation, and definition of lung toxicity scores in consecutive Common Terminology Criteria for Adverse Events (CTCAE) documents have evolved as well. The most recent CTCAE toxicity scores (18) are based on limits of normal, as opposed to formerly used fixed percentage changes, and their usefulness then depends on how reliably the limits of normal have been established. In the meantime, the global lung function initiative (19-21) has developed tools enabling to establish limits of normal for FVC, TLco and TLC based on updated reference values, as opposed to having to resort to data from normative studies driven by European Community for Steel and Coal, that were biased towards male subjects. For women in the age group under study (typically around 55 years old at study entry) normal lung ageing over a 10-year period is seen to impact FVC and TLco, while hardly affecting TLC. In the present study, we report lung function changes in %predicted to assess radiotherapy-induced changes over and above natural decline of lung function with age. We also identified patients with pre-existing lung function abnormality at study entry, to then determine to what extent either RT modality influenced prevalence of lung function abnormality after 10 years.

MATERIAL AND METHODS

We undertook a prospective lung function study on patients enrolled in the TomoBreast randomized clinical trial (NCTxxx) comparing two radiotherapy regimens (CR *vs* TT) for post-operative treatment of breast cancer. The study was approved by the hospital's ethics committee, and all patients signed an informed consent. The trial started in May 2007 and patient recruitment ended August 2011, and has been described in the initial reports (15,16). Eligible patients were women aged 18 years or older, presenting with histologically proven breast carcinoma, operated by breast conserving surgery or mastectomy with clear margins, pathological stage T1-3N0M0 or T1-2N1M0. Exclusion criteria were prior breast or thoracic radiotherapy, pregnancy or lactation, fertility without effective contraception, psychiatric or addictive disorders.

In the CR arm, a dose of 50Gy was delivered in 25 fractions over 5 weeks to the chest wall (mastectomy) or the whole breast (breast conserving surgery) by 6 or 15 MV photons tangential wedged fields and using field-in-field multileaf compensation when doses exceed 105%, and to the supraclavicular, infraclavicular and axillary nodes in case of pN1 status, using an anterior 6MV photons half-beam matched to the tangential fields. Breast conserved patients received an additional boost of 16Gy in 8 fractions over 2 weeks to the initial tumor bed using a direct electron field, i.e. a cumulative dose of 66Gy in 33 fractions over 7 weeks at the tumor bed. Conventional RT at our institution did not specify heart and lung constraints, but avoided exceeding 2 cm central lung distance. In the TT arm, patients were treated using the Helical TomoTherapy®Hi-art system (Madison, WI, US). A total dose of 42Gy in 15 fractions over 3 weeks

was prescribed to the same target volumes as the conventional arm: chest wall in case of mastectomy or whole breast in case of breast conserving surgery, and to the supraclavicular, infraclavicular and axillary nodes in case of pN1 status. A simultaneous integrated boost of 0.6Gy per fraction was prescribed to the tumor bed, i.e., a dose of 51Gy in 15 fractions over 3 weeks at the tumor bed in case of breast conserving surgery. Tomotherapy dose specifications for target volumes breast/chest wall, boost, and lymph node regions were to receive 95%-105% of prescribed dose; dose constraints for heart and ipsilateral lung were respectively V5Gy <10% and V17Gy <7%, contralateral breast V10Gy <5%.

Radiotherapy in any arm started within 6 weeks after breast surgery. Concurrent or sequential adjuvant systemic treatments were allowed. In case of sequential adjuvant treatment with chemotherapy first, radiotherapy started within 3 weeks after completion of the adjuvant chemotherapy. Pulmonary function was assessed prior to radiotherapy, at 3 months after completion of radiotherapy, thereafter yearly for up to 3 years, and one final FU visit at exactly 10 years. Over the first 3 years, lung function measurements were obtained by means of standardized equipment (Vmax20C, CardinalHealth®, Bilthoven, The Netherlands) and using prediction equations applicable to subjects aged 20-80 years (22), to express all parameters in terms of %predicted. For the 10-year FU measurement, a next generation equipment by the same manufacturer was used (MasterScreen PFT, SentrySuite 2.19; Vyaire Medical, Mettawa, IL, USA) with corresponding prediction equations applicable to subjects aged 20-80 years (23).

Lung function parameters included FEV_1, FVC, FEV_1/FVC respectively reflecting overall airway function, pulmonary restriction, and airway obstruction obtained by spirometry. Diffusing capacity was obtained by a single breath carbon monoxide transfer measurement (TLco,

previously referred to as "DLco" in the 3rd version of the CTCAE document). From the same diffusing capacity test, alveolar volume at total lung capacity (V_A) was determined by inert gas dilution. This was done to obtain $Kco=TLco/V_A$, representing diffusing capacity normalized to ventilated alveolar volume; TLco and Kco were adjusted for Hb level by using the multiplicative correction factor for women, (9.38+Hb)/(1.7Hb), assuming Hb is expressed in g/dl. Using a body plethysmograph, residual volume (RV), total lung capacity (TLC) comprising all volumes of air within the thorax, irrespective of whether they are ventilated (i.e., in communication with the mouth) or not; the ratio RV/TLC is commonly used as an index of air trapping. In terms of %predicted, most of the above parameters are expected to decrease in case of deteriorated lung function, except for RV/TLC which is expected to increase.

Statistical analysis

The trial had been powered for the hypothesis that TT could decrease the cumulative incidence of lung and heart toxicity (all grades) from 25 to 5 %, based on the available literature prior to study onset (24,25); this required 118 patients (power=0.80; significance=0.05; two tailed). The heart toxicity, survival and patient outcomes have been reported elsewhere (26). All analyses were performed as treated (MedCalc, Mariakerke, Belgium) accepting statistical significance at $P<0.05$. After assessing normality for all lung function parameters under study, a 1-way repeated measures ANOVA was performed (with group factor CR or TT), where repeated measures included baseline, 3 months, 1 year, 2 years, 3 years, 10 years; Bonferroni adjustments were used for pairwise comparisons. For analyses involving lung dose (V5,V20), non-parametric tests were used (MannWhitney test; Spearman rank correlations). A Fisher's exact test was used to test for differences in the proportion of patients with a given characteristic between the CR and TT arm.

RESULTS

Study population characteristics

Of the 108 patients for whom baseline, 3 month, 1 year, 2 year and 3 year FU measurements had been obtained, 84 patients could be measured at 10-year FU (median[IQR]: 120[118-121] months), when they were aged 64±10(SD)years. Figure 1 shows a break-down of the study population and drop-outs per radiotherapy regimen (CR or TT). Of the 108 patients who could be measured at three years, 9 patients had died by the time of the 10-year FU visit. Out of these 9 patients, the 7 patients without any pre-existing lung condition or smoking status, had a projected median age of 85 years at 10-year FU. Twelve patients were lost to follow-up at the 10-year visit, mainly due to age-related morbidities (n=5), or else because they were monitored at another center (n=2), could not attend because of COVID (n=3), or simply withdrew consent (n=2). Finally, one patient presented relapse with distant metastasis and two patients developed a second primary breast cancer (3/108=2.8%). Since the ANOVA analysis will discard any patient with missing values for either one of the 6 visits, we only report data for the 84 patients for whom valid lung function data could be obtained on all FU visits (grey boxes in Figure 1). We also considered a subpopulation (n=57) by excluding from the entire group (n=84) any patient with a smoking history >10 packyears (n=16; 10 out of 16 were ex-smokers) or with a documented history of respiratory disease (n=11) at study enrolment (27/84=32%).

Treatment effects on lung function and correlation to dose

The evolution of lung function parameters under study over the course of 10 years is shown in Table 1 and expressed in terms of %predicted to describe the lung function decline that is not due to normal ageing. In the entire study population (n=84; Table 1) there was a significant

baseline difference between both treatment arms for FEV_1 and V_A, but not for the parameters of interest to parenchymal damage (FVC, TLco and TLC); in the subgroup without smoking history or respiratory disease, there were no baseline differences at all (Table 2). For the entire group, overall changes between 10 years and baseline (Δ) were similar in CR and TT arms (last column in Table 1). Median [IQR] lung volume exposed to dose exceeding 5Gy (V5) or 20Gy (V20), expressed as a percentage of ipsilateral lung volume was respectively 20.6 [16.8-30.7] % and 10.1 [7.1-15.0] %. When expressed as a percentage of total lung volume, to favor a potential relationship with lung function derived volumes (which measure the entire lung), median V5 and V20 amounted to respectively 10.9 [8.3-15.9] % and 4.9 [3.6-7.5] %. In the entire study cohort, and across treatment arms, there was only one lung function variable showing a significant correlation to lung dose (V5 or V20), namely ΔTLco in %predicted which correlated with V20 (rho= -0.33; p=0.002) and V5 (rho= -0.26; p=0.02).

Treatment effects in patients with no smoking history or respiratory disease

In the subpopulation without any confounding effects from smoking or baseline respiratory disease (Table 2) very similar patterns were observed with respect to the entire group (Table 1) for all parameters under study. For FVC and TLco, this can also be appreciated from Figure 2. The most striking acute decline during the first 3 months after RT is observed for diffusing capacity in the CR arm (TLco; Figure 2B). The TLco deterioration was driven by a smaller volume available for diffusion (V_A) and when normalizing TLco for V_A, the resulting Kco did not significantly change in the entire follow-up period (Table 2). Since changes (Δ) between baseline and 10 years were similar in CR and TT arms, and average($\pm$SD) 10-yr decline in the 3 main lung function parameters can be established for otherwise healthy non-smoking middle aged women : ΔFVC= -13 ($\pm$9) %predicted; ΔTLco= -14 ($\pm$12) %predicted; ΔTLC= -11 ($\pm$9) %predicted. There

was a significant correlation between ΔTLco after 10 years in % predicted and V20 (rho= -0.36; p=0.007), but not V5 (rho= -0.25; p=0.06), in this subgroup of patients with no smoking history or respiratory disease. However, any correlation between V20 and the degree of TLco abnormality at 10 years (expressed in terms of z-score) did not reach significance either (P=0.057 for the entire subgroup and P>0.1 for TT and CR arms, separately).

Because pre-existing lung disease or smoking history cannot be equated to a normal baseline lung function status, we also scrutinized the entire patient cohort for lung function abnormality at baseline. Of those patients with normal lung function (z-score for each variable within 1.64 of the median), we determined which percentage of patients could still be considered normal in terms of these lung function variables 10 years after RT, taking into account the ageing process. The result is shown in Table 3, where the proportion of patients with normal lung function at baseline who were still normal at 10-year FU, did not differ between both RT treatment arms.

DISCUSSION

In this study, we observed the long-term lung function effect in early stage breast cancer patients 10 years after having undergone one of two radiotherapy modalities (15). Despite a slightly greater lung restriction initially (at 3 months) with conventional radiotherapy than with image-guided hypofractionated radiotherapy, this evolved to a similar degree of lung restriction 10 years following either radiotherapy regimen.

The degree of pulmonary restriction over the course of ten years after radiotherapy can be best appreciated from measures of forced vital capacity (FVC) and total lung capacity (TLC, which is the gold standard). In the patient cohort under study, FVC and TLC were normal at baseline, and showed an average decrease of 10-15% predicted. This was the case in the entire study group (Table 1) and in the subgroup with negligible smoking history and no respiratory disease at baseline (Table 2; Figure 2). The lung function variable most sensitive to changes in lung parenchyma is TLco, which includes, but is not limited to, the volumetric effect of restriction since it measures the rate of carbon monoxide uptake into the pulmonary capillary bed. In this respect, the comparable TLco decrease to that in FVC or TLC does point to a predominant role for a purely volumetric RT-induced restriction on the lung's diffusing capacity (as opposed to a deterioration in the capillary blood compartment). The diffusing capacity decreases seen here were of similar magnitude to those typically observed after a volume reduction of the lung by lobectomy (27,28), attesting to a considerable reserve capacity of the lungs at rest.

A 11-17% loss with respect to the lung's predicted gas exchanging capabilities is acceptable, given the efficacy of radiotherapy as a post-operative treatment for breast cancer (29). Diffusing capacity is also commonly used in the follow-up of RT induced lung toxicity, where the most recent CTCAE document (v5 dated Nov27th, 2017; 18) stipulates that grade 1 toxicity corresponds to a TLco decrease from baseline ranging 3 to 5 ml/min/mmHg. For a 60-year old female of average height this corresponds to a decrease ranging 15 to 24% predicted (where a 0% predicted change accounts for the normal TLco decrease with ageing). Hence, we may conclude that the TLco decreases observed in this study are of the order of what would be considered grade 1 lung toxicity.

In the past decade, the Global Lung Function Initiative has promoted sophisticated statistical techniques to determine lung function abnormality (19) and has emphasized that lung function abnormality should be based on z-scores (22). Typically, patients with z-scores for FVC, TLco or TLC below -1.64 (or above +1.64 for RV/TLC) would be considered abnormal in terms of that lung function variable. Using this approach, we confirmed that large percentages of the patients who were normal at baseline, were still normal after 10-yr FU (Table 3). In fact, the parameter indicating the lowest percentage of patients remaining normal (V_A : 74% in the CR arm) is known to be more dependent on patient cooperation during the test, and can be artificially low due to incomplete inspiration of the test gas. The fact that TLC (which essentially measures the same degree of lung inflation as V_A but with a different technique) remained normal in 90-98% of the patients with a normal baseline TLC, is reassuring. Importantly, there was no statistically significant difference between the proportion of subjects remaining normal after 10-yr FU in either treatment arm.

Possibly because of the low V20 range and the mild degree of incurred lung function defects, we did not detect consistent correlations between V20 and lung function changes after 10-yr FU, except for TLco. This is in overall agreement with similar studies in breast cancer patients (30,31) with long follow-up periods, but where correlation was only interrogated for VC or FVC. In the present study, TLco was seen to decrease more for subjects exposed to higher V20 levels, also in line with an earlier report, but where average V20 was almost double that shown here (32).

Our data can be set against previous reports of RT-induced changes in breast cancer patients, even though the effect of pre-existing pulmonary disease cannot always be identified. For instance, Theuws et al (33) observed only marginal TLco changes at the end of their 1.5 year

follow-up period in 51 patients (where 30% of the patients had pre-existing lung condition). Erven et al (12) reported a 10% decrease from baseline of total lung capacity and diffusing capacity at 8-10 years after conventional radiotherapy in 48 patients, which included active smokers or ex-smokers; similar results were obtained by Blom-Goldman et al (31) in 56 patients. In Ooi et al (34), where respiratory disease or an abnormal chest radiograph were used as exclusion criteria, FVC, TLC and TLco were seen to decrease by 10% predicted in a 1 year follow-up period of 30 breast cancer patients. The 10-year FU observation window presented here confirms earlier observations of lung restriction for the two different radiotherapy regimens under study. Critical to their interpretation, our lung function measurements were scrutinized for any potential operational changes over the 10-year period, and up-to-date reference values were used that can reliably account for natural ageing in a wide age range.

Study limitations

By comparing TT and CR treatment arms, we inherently assumed that normal and hypofractionation are equivalent in terms of treatment effect and toxicity, as indicated by large UK and Canadian clinical trials (6,7). At the time of this trial, normofractionation was our standard of care. Since treatment on tomotherapy would take longer, we chose mild hypofractionation for the experimental arm to limit total machine time. There are some limitations that are intricately related to long-term follow-up studies, such as equipment changes. While equipment certainly evolves more rapidly in the realm of radiotherapy than in lung function testing, lung function measurement and analysis methodology has also evolved, allowing a more rigorous approach when dealing with laboratory equipment replacement which typically occurs every 10 years (35). A final limitation concerns the inclusion of patients with pre-existing lung disease, ex-smokers and active smokers, but in insufficient numbers for them to be separately assessed. Meta

analysis has shown that the estimated absolute risks of lung cancer or cardiac mortality at >10 years from modern radiotherapy for breast cancer increases from less than 1% in non-smokers to a few percentage points if smoking continues (29). This implies that for almost 80% of the women in the present study (57 never-smokers and 10 ex-smokers out of 84), the radiotherapy-induced risk is much smaller than its benefit, which is complementary to the relatively mild deterioration in lung function found here.

In summary, this study found a mild degree of pulmonary restriction 10-years after radiotherapy treatment for early stage breast cancer. The lung function effect was of comparable magnitude for the hypofractionated and conventional radiotherapy treatment. The large majority of patients with normal pulmonary function at baseline remained within the limits of normal after 10 years follow-up.

REFERENCES

1. Bekelman JE, Sylwestrzak G, Barron J, **et al.** Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. *JAMA* 2014;312:2542-2550.
2. Cardoso F, Kyriakides S, Ohno S, **et al.**; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2019;30:1194-1220.
3. Murray Brunt A, Haviland JS, Wheatley DA, **et al.**; FAST-Forward Trial Management Group. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* 2020;395:1613-1626.
4. Machiels M, Weytjens R, Bauwens W, **et al**. Accelerated Adaptation of Ultrahypofractionated Radiation Therapy for Breast Cancer at the Time of the COVID-19 Pandemic. *Clin Oncol (R Coll Radiol)* 2021;33:e166-e171.
5. Yarnold J, Ashton A, Bliss J, **et al.** Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* 2005;75:9-17.
6. Owen JR, Ashton A, Bliss JM, **et al.** Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006;7:467-471.
7. Whelan TJ, Pignol JP, Levine MN, **et al.** Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513-520.
8. Haviland JS, Owen JR, Dewar JA, **et al.** The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; 14: 1086–1094.
9. 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; 70:1460-1467.

10. Lind PA, Rosfors S, Wennberg B, **et al.** Pulmonary function following adjuvant chemotherapy and radiotherapy for breast cancer and the issue of three-dimensional treatment planning. *Radiother Oncol* 1998; 49:245-254.
11. Jaén J, Vázquez G, Alonso E, **et al.** Changes in pulmonary function after incidental lung irradiation for breast cancer: A prospective study. *Int J Radiat Oncol Biol Phys* 2006; 65:1381-1388.
12. Erven K, Weltens C, Nackaerts K, **et al.** Changes in pulmonary function up to 10 years after locoregional breast irradiation. *Int J Radiat Oncol Biol Phys.* 2012; 82:701-707.
13. Sánchez-Nieto B, Goset KC, Caviedes I, **et al.** Predictive models for pulmonary function changes after radiotherapy for breast cancer and lymphoma. *Int J Radiat Oncol Biol Phys* 2012;82:e257-264.
14. Vandevoorde J, Verbanck S, Schuermans D **et al**. Forced vital capacity and forced expiratory volume in six seconds as predictors of reduced total lung capacity. *Eur Respir J* 2008;31:391-395.
15. XXX
16. XXX
17. XXX
18. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events Version 5.0, DCTD, NCI, NIH, DHHS (http://ctep.cancer.gov), Publish Date: November 27, 2017.
19. Quanjer PH, Stanojevic S, Cole TJ, **et al.**; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012 Dec;40(6):1324-43. doi:10.1183/09031936.00080312.
20. Stanojevic S, Graham BL, Cooper BG, **et al.**; Global Lung Function Initiative TLCO working group; Global Lung Function Initiative (GLI) TLCO. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J* 2017;50:1700010. Erratum in: *Eur Respir J* 2020 Oct 15;56(4).
21. Hall GL, Filipow N, Ruppel G, Okitika T, Thompson B, Kirkby J, Steenbruggen I, Cooper BG, Stanojevic S; contributing GLI Network members. Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry. *Eur Respir J* 2021;57:2000289.

22. Verbanck S, A Van Muylem, Schuermans D, **et al.** Transfer factor, lung volumes, resistance and ventilation distribution in healthy adults. *Eur Respir J* 2016;47:166-176.
23. Hanon S, Vanderhelst E, Vincken W, **et al.** Peak In- and Expiratory Flow Revisited: Reliability and Reference Values in Adults. *Respiration* 2021;100:11-18.
24. Wennberg B, Gagliardi G, Sundbom L, **et al.** Early response of lung in breast cancer irradiation: radiologic density changes measured by CT and symptomatic radiation pneumonitis. *Int J Radiat Oncol Biol Phys* 2002; 52:1196-1206.
25. Lind PA, Pagnanelli R, Marks LB, **et al.** Myocardial perfusion changes in patients irradiated for left-sided breast cancer and correlation with coronary artery distribution. *Int J Radiat Oncol Biol Phys* 2003;55:914-920.
26. Van Parijs H, Vinh-Hung V, Fontaine C, **et al.** Cardiopulmonary-related patient-reported outcomes in a randomized clinical trial of radiation therapy for breast cancer. *BMC Cancer* 2021;21:1177.
27. Bolliger CT, Jordan P, Solèr M, **et al.** Pulmonary function and exercise capacity after lung resection. *Eur Respir J* 1996;9:415-421.
28. Gu Z, Wang H, Mao T, **et al.** Pulmonary function changes after different extent of pulmonary resection under video-assisted thoracic surgery. *J Thorac Dis* 2018;10:2331-2337.
29. Taylor C, Correa C, Duane FK, **et al**; Early Breast Cancer Trialists' Collaborative Group. 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;35:1641-1649.
30. Vågane R, Bruland ØS, Fosså SD, **et al.** Radiological and functional assessment of radiation-induced pulmonary damage following breast irradiation. *Acta Oncol*. 2008;47:248-254.
31. Blom-Goldman U, Svane G, Anderson M, **et al.** Long-term functional and radiological pulmonary changes after radiation therapy for breast cancer. *Acta Oncol.* 2014;53:1373-1379.
32. Lind PA, Wennberg B, Gagliardi G, **et al.** ROC curves and evaluation of radiation-induced pulmonary toxicity in breast cancer. *Int J Radiat Oncol Biol Phys* 2006;64:765-770.

33. Theuws JC, Muller SH, Seppenwoolde Y, **et al.** Effect of radiotherapy and chemotherapy on pulmonary function after treatment for breast cancer and lymphoma: A follow-up study. *J Clin Oncol* 1999;17:3091-3100.
34. Ooi GC, Kwong DL, Ho JC, **et al.** Pulmonary sequelae of treatment for breast cancer: a prospective study. *Int J Radiat Oncol Biol Phys* 2001;50:411-409.
35. Verbanck S, Schuermans D, Thompson BR, **et al**. Aligning Lung Function Equipment and Reference Values in Adults. *Respiration* 2019;98:246-252.

FIGURE LEGENDS

Figure 1 :

Flow chart of patients recruited for this study with subgroups and drop-outs. Median ages are also displayed for drop-out patients per category. CR: conventional radiotherapy; TT: hypofractionated tomotherapy. Grey boxes are the patients who could be evaluated at 10 years of follow-up.

Figure 2 :

Panel A: Forced vital capacity (FVC, in %predicted) in the patients with negligible history of respiratory disease or smoking (n=57), at baseline and up to 10 years after conventional radiotherapy (CR; n=23) or hypofractionated tomotherapy (TT; n=34). Average±SE. Also indicated: any significant difference from baseline in the CR (*) or TT group (#).

Panel B: Diffusing capacity or carbon monoxide transfer factor (TLco, in %predicted); same representation as panel A.

Table 1 : Lung function in the study population, including smokers and patients with diagnosed respiratory disease (n=84)

		TT (n=44)							CR (n=40)								
		Baseline	3mo	1yr	2yr	3yr	10yr	Δ	Baseline	3mo	1yr	2yr	3yr	10yr	Δ	P-value[a]	P-value[b]
Patient characteristic																	
Aged>50y at 10yr FU	(%)	95%							93%							0.6	
Left breast tumor	(%)	61%							48%							0.2	
Locoregional RT	(%)	23%							25%							0.8	
Chemotherapy	(%)	45%							48%							0.9	
Hormone therapy	(%)	84%							85%							0.9	
V20 (%ipsi lung)	median	9.0							11.3							0.004	
	(IQR)	5.7 - 12.4							9.2 - 18.3								
V5 (%ipsi lung)	median	20.6							21.6							0.4	
	(IQR)	16.2 - 30.2							18.3 - 35.6								
Spirometry																	
FEV_1 (%pred)	mean	108	105	103	102 *	101 *	96 *	-12	99	95	97	93 *	94	85 *	-14	0.01	0.5
	(SD)	(2)	(2)	(2)	(2)	(2)	(3)	(1)	(3)	(2)	(3)	(3)	(3)	(3)	(2)		
FVC (%pred)	mean	110	107	105 *	104 *	102 *	95 *	-14	103	100	101	98 *	98 *	88 *	-15	0.065	0.6
	(SD)	(2)	(2)	(2)	(2)	(2)	(2)	(1)	(3)	(2)	(2)	(2)	(2)	(2)	(2)		
FEV_1/FVC (%pred)	mean	99	98	98	98	98	100	1	95	95	96	95	96	95	0	0.046	0.5
	(SD)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(2)	(1)	(1)	(2)	(2)	(1)		
Diffusion Capacity																	
TLco (%pred)	mean	104	103	100	101	101	93 *	-11	99	92 *	94	93 *	94	84 *	-14	0.11	0.2
	(SD)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(2)	(2)	(3)	(2)	(3)	(2)		
VA (%pred)	mean	95	94	90 *	92 *	92 *	89 *	-6	90	86 *	87	85 *	86 *	81 *	-9	0.035	0.08
	(SD)	(2)	(2)	(2)	(2)	(2)	(2)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(1)		
Kco (%pred)	mean	96	97	97	97	97	94	-3	95	93	93	95	94	92	-3	0.7	0.8
	(SD)	(2)	(2)	(2)	(2)	(2)	(2)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)		
Bodyplethysmography																	
TLC (%pred)	mean	110	109	103 *	106	103 *	100 *	-10	107	101 *	99 *	100 *	101 *	97 *	-10	0.2	0.9
	(SD)	(2)	(2)	(2)	(2)	(1)	(2)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)		
RV/TLC (%pred)	mean	105	107	102	107	105	111	7	109	105	101	108	107	117	8	0.3	0.8
	(SD)	(2)	(3)	(3)	(3)	(3)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)		

Abbreviations: %pred:percent predicted; FEV_1:forced expiratory volume in 1 second; FVC:forced expiratory vital capacity; Kco=TLco/VA;
RT : radiation therapy; TLC : total lung capacity; TLco : transfer factor for carbon monoxide; VA : alveolar volume at total lung capacity.
Δ: Value at 10 years minus that at baseline (in %pred).
P-value[a] : significant difference between baseline values (TT vs CR)
P-value[b] : significant difference between changes from baseline (TT vs CR)

Table 2 : Lung function in the study population excluding smokers and patients with diagnosed respiratory disease (n=57)

		TT (n=34)							CR (n=23)								
		Baseline	3mo	1yr	2yr	3yr	10yr	Δ	Baseline	3mo	1yr	2yr	3yr	10yr	Δ	P-value[a]	P-value[b]
Patient characteristic																	
Aged>50y at 10yr FU	(%)	94%							96%							0.8	
Left breast tumor	(%)	56%							39%							0.2	
Locoregional RT	(%)	29%							26%							0.8	
Chemotherapy	(%)	53%							43%							0.5	
Hormone therapy	(%)	82%							83%							1.0	
V20 (%ipsi lung)	median	9.8							11.8							0.040	
	(IQR)	6.3 - 14.6							9.4 - 22.0								
V5 (%ipsi lung)	median	24.8							23.0							0.9	
	(IQR)	17.3 - 30.7							18.4 - 36.9								
Spirometry																	
FEV_1 (%pred)	mean	110	108	106	106 *	103 *	100 *	-10	104	101	104	99 *	100	92 *	-12	0.14	0.4
	(SD)	(2)	(3)	(3)	(2)	(2)	(3)	(2)	(4)	(3)	(3)	(3)	(3)	(4)	(2)		
FVC (%pred)	mean	111	109	107	106 *	104 *	98 *	-13	105	101	103	99	99 *	91 *	-14	0.14	0.5
	(SD)	(2)	(3)	(3)	(2)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(3)	(4)	(2)		
FEV_1/FVC (%pred)	mean	99	98	99	99	99	101	2	99	99	100	99	101	100	1	0.7	0.9
	(SD)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)		
Diffusion Capacity																	
TLco (%pred)	mean	106	104	101	101	102	94 *	-12	104	95 *	96 *	95 *	96 *	87 *	-17	0.6	0.12
	(SD)	(3)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(2)	(2)	(3)	(2)	(3)	(3)		
VA (%pred)	mean	96	95	92 *	93	93 *	90 *	-7	91	87 *	88	85 *	87 *	82 *	-9	0.13	0.12
	(SD)	(2)	(2)	(2)	(2)	(2)	(2)	(1)	(2)	(2)	(2)	(2)	(2)	(3)	(1)		
Kco (%pred)	mean	97	97	97	96	97	95	-2	99	95	95	96	96	94	-5	0.5	0.3
	(SD)	(2)	(3)	(2)	(2)	(2)	(2)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(3)		
Bodyplethysmography																	
TLC (%pred)	mean	112	111	105 *	108	104 *	102 *	-10	107	101 *	98 *	99 *	101	95 *	-12	0.15	0.4
	(SD)	(2)	(2)	(2)	(3)	(2)	(2)	(1)	(2)	(2)	(2)	(2)	(3)	(3)	(2)		
RV/TLC (%pred)	mean	104	105	100	104	102	109	5	106	103	94	104	105	110	4	0.7	0.9
	(SD)	(3)	(1)	(3)	(3)	(3)	(2)	(3)	(3)	(3)	(4)	(3)	(4)	(3)	(3)		

Abbreviations as in Table 1.

Δ: Value at 10 years minus that at baseline (in %pred).

P-value[a] : significant difference between baseline values in TT and CR arms

P-value[b] : significant difference between changes from baseline in TT and CR arms

* Significantly different from baseline (Bonferroni; p <0.05).

Table 3 : Degree of lung function abnormality after 10 yr radiotherapy.

	TT (n=44)		CR (n=40)		
	normal at baseline (n)	normal at 10 yr FU (% normal at baseline)	normal at baseline (n)	normal at 10 yr FU (% normal at baseline)	P-value
Spirometry					
Subjects with FEV_1 z-score < -1.64	41	95%	33	79%	0.07
Subjects with FVC z-score < -1.64	43	93%	37	95%	1.0
Subjects with FEV_1/FVC z-score < -1.64	43	95%	30	90%	0.4
Diffusion Capacity					
Subjects with TLco z-score < -1.64	41	95%	34	97%	1.0
Subjects with VA z-score < -1.64	38	89%	27	74%	0.2
Subjects with Kco z-score < -1.64	39	92%	35	100%	0.2
Bodyplethysmography					
Subjects with TLC z-score < -1.64	42	98%	39	90%	0.2
Subjects with RV/TLC z-score > +1.64	37	92%	30	93%	1.0

P-value : signficant difference between TT and CR in prevalence of abnormality at 10 yr FU