

NEW APPROACHES FOR THE PREVENTION OF RADIATION LUNG DAMAGE IN BREAST CANCER

Ph.D. Thesis

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- II. **Varga Z.**, Cserhádi A., Kelemen Gy., Boda K., Thurzó L., Kahán Zs.
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- Kahán Z., Csenki M., **Varga Z.**, Szil E., Cserhádi A., Balogh A., Gyulai Z., Mándi Y., Boda K., Thurzó L.
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List of abbreviations

2D	two-dimensional
3D	three-dimensional
ANOVA	analysis of variance
BMI	body mass index
CI	confidence interval
CLD	central lung distance
CT	computed tomography
DRR	digitally reconstructed radiograph
DVH	dose-volume histogram
ICRU	International Commission on Radiation Units and Measurements
IMN	internal mammary lymph nodes
MDC _{HC}	mean lung density changes at the level of the head of the clavicle
MDC _{LHV}	mean lung density changes at the level of the left heart ventricle
MHD	mean dose to the heart
MLD	mean lung dose
OAR	organ at risk
OR	odds ratio
PTV	planning target volume
V _{5Gy}	volume receiving more than 5 Gy
V _{20Gy}	volume receiving more than 20 Gy
V _{25Gy}	volume receiving more than 25 Gy
V _{30Gy}	volume receiving more than 30 Gy
V _{95%-107%}	volume receiving at least 47.5 Gy, but less than 53.5 Gy

1. Introduction

The various forms of adjuvant therapy including postoperative irradiation and systemic therapy in breast cancer, contribute to the decreasing mortality rate among the affected population (1, 2). Adjuvant radiotherapy is a standard form of treatment after breast-conserving surgery, and is sometimes practised after mastectomy, too (3, 4). Nonetheless, radiotherapy may cause long-term toxicity such as radiation-induced pneumonitis and fibrosis of the lung. Early radiation-induced symptoms arise within 6 months after the completion of radiotherapy, and may later progress to a chronic fibrotic status (5, 6). An older age, the irradiation of a larger lung volume and a higher mean lung dose have been found to be risk factors for the occurrence of radiogenic lung damage (7-11). In some reports, the simultaneous administration of tamoxifen during radiotherapy was associated with the development of early or late radiation lung damage (12-14), whereas no such relationship was observed in other studies (8, 10, 15-17). No similar data as yet have been published with the use of aromatase inhibitors during breast radiotherapy except one small study (18). CT-based 3D conformal radiotherapy is essential to control the radiation dose to the organs at risk (OARs) and to improve the dose-distribution, within the target volume that determines efficiency. There are different possibilities to reduce the radiation exposure of the ipsilateral lung. The simplest way to protect the OARs during breast radiotherapy is individual patient positioning. It has been observed that a prone position during breast radiotherapy results in a substantially lower dose to the OARs such as the ipsilateral lung (19-23) and the heart (19, 22), with the additional advantage of improved dose homogeneity (19, 20, 23). This mode of positioning has been shown to be feasible (24, 25), even in obese patients (22), and to provide a similar long-term outcome and toxicity as with standard supine tangents (25, 26).

2. Aims

2.1. A prospective analysis of the risks of early and late radiogenic lung damage in early breast cancer patients after conformal radiotherapy in relation to the different patient- (age, smoking, systemic therapy) and treatment-associated (dose to the ipsilateral lung, irradiation of the nodes) features.

2.2. A prospective study to compare radiotherapy in the prone position with our usual technique in the supine position with excellent repositioning accuracy. The identification of those patients who benefit most from prone positioning by means of dosimetry (dose homogeneity and protection of the OARs) and feasibility (including repositioning accuracy).

3. Patients and methods

3.1. The risk of early and late lung damage after conformal radiotherapy

3.1.1. Patients

Between 11/2001 - 08/2004 and 01/2006 - 05/2008, patients after curative surgery for breast cancer who required radiotherapy were recruited at our department. Patients with prior malignancy, pulmonary or autoimmune disease or any other significant health problem, or who were on glucocorticoid therapy, were excluded. The initial surgery was either mastectomy or breast-conserving surgery, with sentinel lymph node biopsy or/and axillary lymph node dissection.

Data were collected on the smoking habits, with the participants categorized as past or present smokers or non-smokers.

3.1.2. Methods

Radiotherapy

CT-based three-dimensional (3D) treatment planning and conformal radiotherapy was in all cases performed with the patient in a supine position. Briefly, CT images were acquired at every 1 cm throughout the entire planning volume. The target volume and organs at risk (OARs) were contoured on the CT slices in the radiotherapy planning system. The planning target volume (PTV) coverage was analyzed via the dose-volume histograms (DVHs) and isodose visualization. Local (operated breast or chest wall) or

locoregional (the former together with coverage of any of the following regions: axillary, supraclavicular and internal mammary lymph nodes [IMNs]) radiotherapy was chosen according to the local protocol. A standard technique of irradiation was used to cover the operated breast/chest wall and the IMNs with tangential fields, and from 01/2005, individually weighted 6 or 15-MV segmental fields were superimposed on the tangential fields, using a multileaf-collimator for better dose homogeneity. The axillary and supraclavicular nodes were irradiated with a direct photon field. The tumor bed boost was delivered with either 6-MV photon or 8-15-MeV electron fields. The radiation dose to the remaining breast parenchyma/chest wall and to the lymph nodes, if indicated, was 25x2 Gy (prescribed to the mean of the PTV); a tumor bed boost of 5-8x2 Gy was delivered when necessary. OAR constraints were used as previously described, and the volume of the ipsilateral lung receiving more than 20 Gy [$V_{20\text{Gy}}$] and the mean lung dose [MLD] were registered for the purpose of this study. The radiotherapy was delivered with a linear accelerator in 5 fractions per week. Although the technical background changed due to modernization in 2005, the use of different planning and positioning systems or field-shaping techniques did not influence the radiotherapy protocol significantly.

Evaluation of radiogenic lung damage

At 3 months and at 1 year following the completion of the radiotherapy, clinical follow-up visits with special attention to pulmonary symptoms (fever, cough and dyspnea) and diagnostic CT examinations were performed. The CT scans at these stages were compared with those provided for radiotherapy-planning purposes according to the accepted criteria (9). The evaluation was performed independently by 2 physicians. The categories of pneumonitis of grade I or fibrosis of grade I were used to describe the new appearance of inflammatory or fibrotic abnormalities in the radiation fields at the two time points, regardless of whether or not the patient simultaneously developed specific clinical signs and symptoms, according to the Common Toxicity Criteria version 2.0 (Figs. 1 and 2).

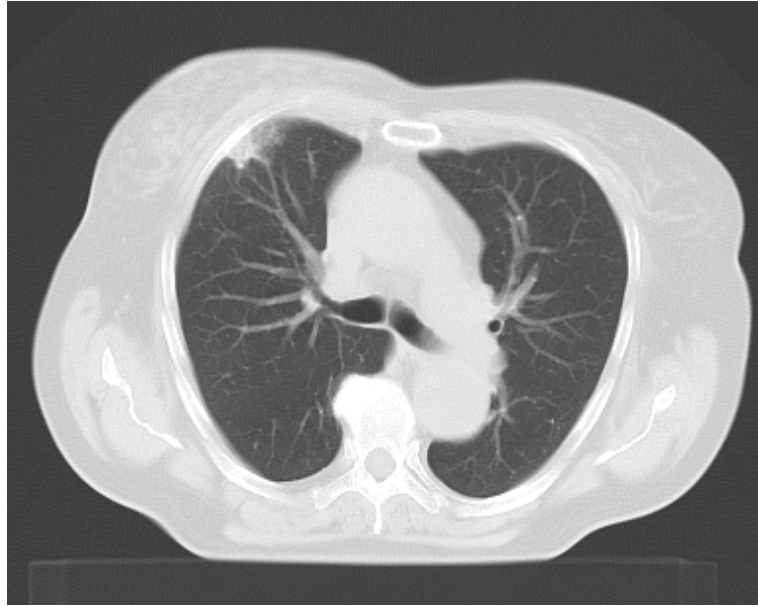


Figure 1 Typical inflammatory lesion in the CT, 3 months after the radiotherapy

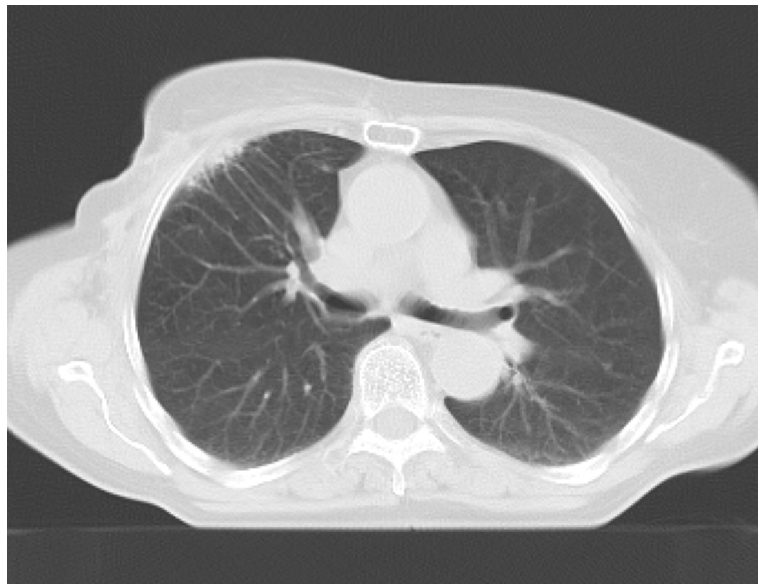


Figure 2 Typical fibrotic lesion in the CT, 1 year after the radiotherapy

On these occasions, the mean lung density changes were measured at the levels of the left heart ventricle (MDC_{LHV}) and the head of the clavicle (MDC_{HC}) too (Fig. 3).

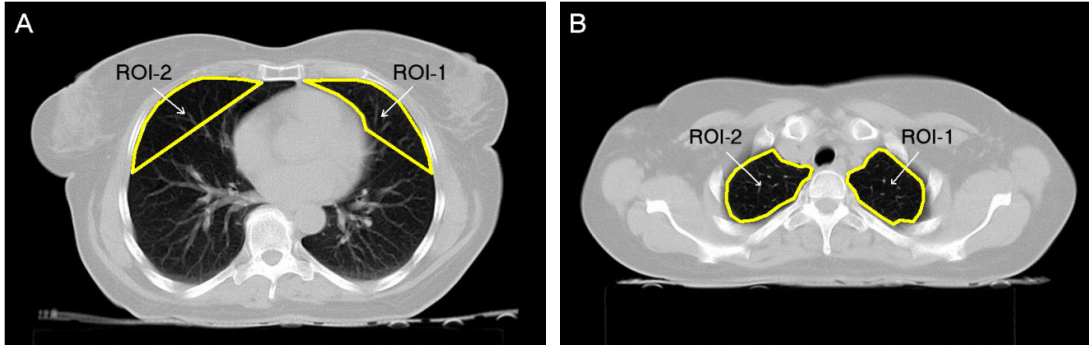


Figure 3 Evaluation of lung density in the CT slices at the levels of the left heart ventricle (A) and the superior aspect of the head of the clavicle (B). Mean lung density was measured in the region of interest (ROI) as outlined on both sides, and for the accurate assessment of lung density changes, the ipsilateral lung density was corrected by that on the contralateral side.

The CT examinations were not performed 1 year after the radiotherapy in 15 cases because of the progression of the breast cancer or some other disease (n=9), the lack of compliance of the patient (n=5) or a car accident (n=1).

Statistical analysis

The various patient- and radiotherapy-related characteristics were examined in the 4 groups of patients according to the presence or absence of radiogenic lung damage by univariate statistical methods, one-way ANOVA and the chi-square tests being used for the continuous and categorical variables, respectively. The changes in lung density across the groups were tested by repeated measures ANOVA. The relationships of age and the MLD were examined by analysis of covariance. The associations between the severity of radiation lung damage versus the age of the patient or the MDCs were analyzed by independent samples t-test.

Logistic regression models were applied to examine the potential risk factors for the occurrence of early and late CT changes with or without clinical symptoms. First, binary univariate logistic regression models were utilized separately, followed by the multivariate logistic regression model to examine the joint effects and interactions. A stepwise procedure was employed with a likelihood ratio test. SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL) was applied for statistical analysis.

3.2. The effects of individual positioning on the radiation exposure of the risk organs

3.2.1. Patients

The study had been approved by the Institutional Review Board of the University of Szeged, and all the enrolled patients gave their written informed consent before being registered as participating in the study.

Early breast cancer patients after surgery requiring only radiotherapy of the operated breast were included in the study. No restriction existed regarding the size of the breast or the patient.

In the first phase of the study (n=20), although radiotherapy planning was performed in both positions, all patients received radiotherapy in the supine position. The 41 patients enrolled in the second phase were randomized to radiotherapy in the prone *vs.* the supine position, but the position for radiotherapy randomized to the patient was blinded to the physician who performed the contouring.

3.2.2. Methods

Radiotherapy

The patients were positioned on the supine thorax and the prone breast modules of the AIO (All In One) SolutionTM (ORFIT, Belgium) system, which contains special cushion sets fixed to a universal baseplate. In the supine position, the patient was laid on a 15° thorax wedge cushion with both arms elevated, resting on an arm support, and held on an adjustable grip pole. The head was placed in the head support secured to a supplementary baseplate attached to the thorax cushion. In the prone position, the head was resting on a pillow, both arms were placed superolaterally, supported by the cranial part of the prone breast cushion, and the target breast was hanging across the semicircular aperture of the platform. The patient was rotated slightly so as to allow the ipsilateral chest wall to extend into the aperture. A thermoplastic mask (5-point fixation, breast precut; ORFIT, Belgium) was applied in the supine position, moulded around the chin, the neck, the thorax (excluding the target breast) and the abdomen. The opposite breast was covered with the mask and carefully positioned away from the radiation fields. Mask fixation was not used in the prone position, but a polyfoam wedge was placed under the contralateral breast in order to displace it. Based on the experience gained during the first phase of the study, in the second 41 patients, a different polyfoam wedge was applied as a new development of the AIO system, for better protection of the opposite breast (Fig. 4).

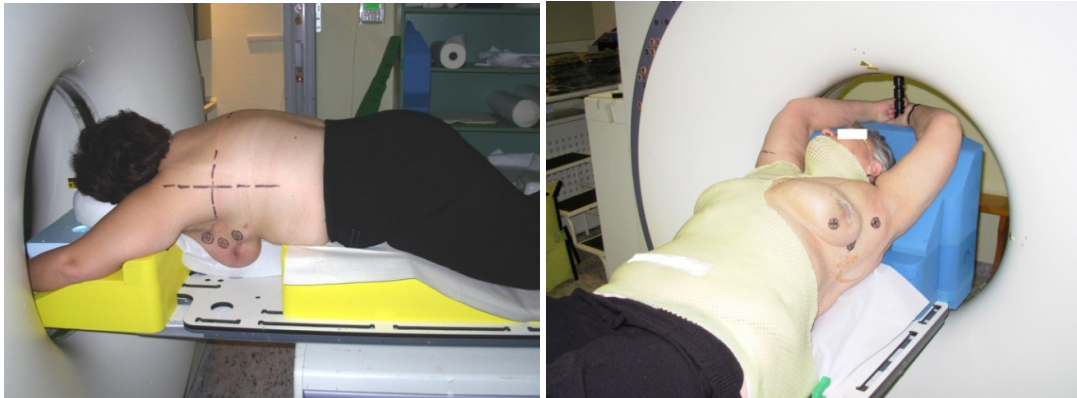


Figure 4 Typical prone and supine positioning during breast radiotherapy

Positioning landmarks were drawn on the skin or the mask, using two lateral lasers and one overhead laser. All patients were scanned on a Somatom Emotion 6 CT simulator (Siemens, Germany) in both positions. The planning target volume (PTV) and OARs were contoured on the CT slices throughout the entire planning volume in the XIOTM (CMS) treatment planning system, according to the local protocol (9). The PTV was defined as the entire breast delineated on the CT data set, extending to within 4 mm of the skin surface. Treatment plans were developed by applying conventional 6 MV tangential photon fields set up isocentrically, and median 2 (1-3) individually weighted 6/15 MV segmental fields superimposed on the tangential fields by using a multileaf collimator. Wedges were used in almost all cases. A mean dose to the PTV of 50 Gy, and a uniform distribution ($\pm 10\%$) of the prescribed dose to 95% of the PTV, were aimed at. Dose homogeneity within the PTV was characterized by the volume of the breast receiving at least 47.5 Gy, but less than 53.5 Gy ($V_{95-107\%}$). The radiation exposure of the OARs (the volume of the ipsilateral lung receiving more than 20 Gy [V_{20Gy}], the mean lung dose [MLD], the mean dose to the heart [MHD], the volume of the heart receiving more than 25 or 30 Gy [V_{25Gy} and V_{30Gy}], the volume of the contralateral breast receiving more than 5 Gy [V_{5Gy}] and the mean dose to the contralateral breast) was registered in both positions. The central lung distance (CLD) and breast separation (the distance between the medial and lateral beam entry points) were determined in the supine position as measures of the patient anatomy.

Evaluation of repositioning accuracy

The objectives in the second phase of the study were patient adherence to the protocol and repositioning accuracy and toxicity during radiotherapy. Prior to the commencement of radiotherapy, the position of the isocenter in the patient was checked under the CT simulator. The necessary displacement in 3D was registered as the first datum of the repositioning accuracy. The radiotherapy was delivered with a linear accelerator (Primus, Siemens) in 5 fractions per week. The accuracy of patient repositioning during radiotherapy was checked 3 times per week with an electronic portal imaging device (BeamviewTM vs. 2.2, Siemens), with the help of radiopaque markers placed on the skin/mask as reference markers. (The dose delivered by the portal imaging was taken into consideration in the calculation of the final dose received by the patient.) One portal image for one of the tangential beams was recorded, and compared with the corresponding beam's eye view digitally reconstructed radiograph (DRR) generated from the planning system (Fig. 5). The need to correct the position of the table in 2D was established and recorded by one or other of two physicians. Analysis of each port image involved determination of the distances between the radiopaque skin markers, and measurements of the CLD, the lung area included in the field, the central flash distance and the inferior central margin (27, 28) (Fig. 5). The action level was set at 3 mm. Systematic and random errors generated from the 3D vector of displacement during the CT simulation and the 2D vector of displacement during the radiotherapy were calculated according to conventional definitions (29, 30). Acute skin reactions (graded by the CTC AE vs. 3.0) were compared in 41 patients randomized to radiotherapy the prone vs. the supine position, at the end of the whole breast irradiation.

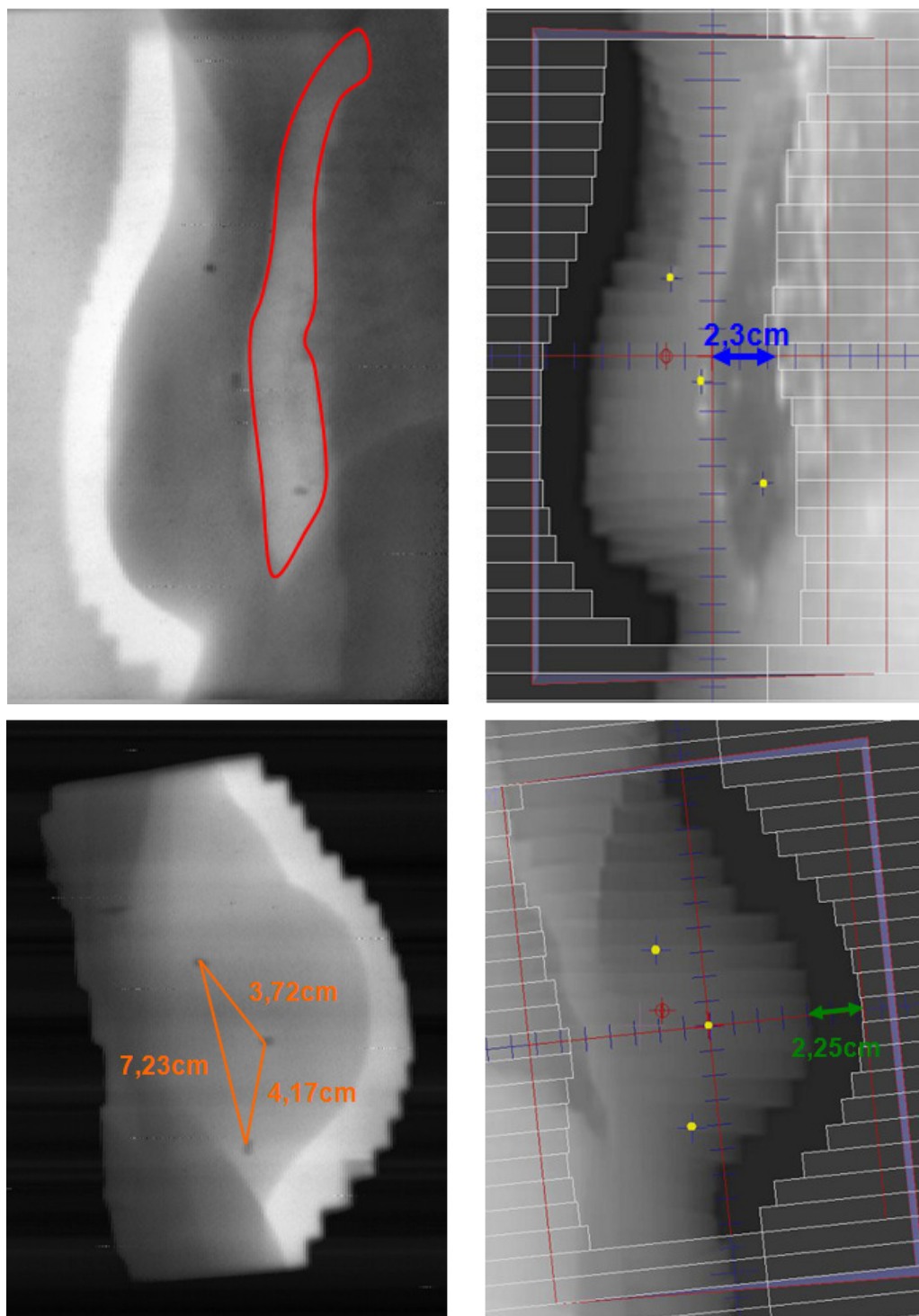


Figure 5 Portal images and DRRs; the analysis of the portal images involved the determination of the lung area included in the field, and measurements of the CLD, the distances between the radiopaque skin markers and the central flash distance.

Statistical analysis

The relations between the data obtained by analysis of the radiotherapy plans and repositioning accuracy *vs.* the patient characteristics were analyzed with the aid of the Student t-test, the chi-square test, regression analysis, ANOVA and logistic regression. Statistical analysis was performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, IL).

4. Results

4.1. The risk of early and late lung damage after conformal radiotherapy

4.1.1. General statistics

Altogether 328 patients were enrolled into the study. The main characteristics of the patients who participated are listed in Table 1.

	Control (n=90)	Taxane (n=79)	Tamoxifen (n=77)	Aromatase inhibitor (n=82)	p
<i>Age (mean±SE, years)</i>	62.4±1.0	51.1±1.1	56.6±1.2	66.3±0.9	<0.0001
<i>Irradiated volume</i>					
<i>Breast</i>	64 (71.1%)	50 (63.3%)	46 (59.7%)	55 (67.1%)	0.449
<i>Chest wall</i>	26 (28.9%)	29 (36.7%)	31 (40.3%)	27 (32.9%)	
<i>Irradiation of the regional lymph nodes</i>					
<i>Yes</i>	16 (17.8%)	66 (83.5%)	22 (28.6%)	22 (26.8%)	<0.0001
<i>No</i>	74 (82.2%)	13 (16.5%)	55 (71.4%)	60 (73.2%)	
<i>MLD (Gy)</i>	8.9±0.3	14.1±0.5	10.7±0.5	10.0±0.4	<0.0001
<i>V_{20Gy} (%)</i>	16.9±0.7	29.0±1.1	21.1±1.3	19.7±1.0	<0.0001
<i>Present or past smokers</i>	38 (42.2%)	29 (36.7%)	38 (49.4%)	24 (29.3%)	0.052
<i>Non-smokers</i>	52 (57.8%)	50 (63.3%)	39 (50.6%)	58 (70.7%)	

Table 1 Associations of the patient- and radiotherapy-related characteristics of the study population and the various forms of systemic therapy

The mean age of the study population was 59.4±0.6 (28.2-87.1) years. The vast majority (96%) of the tumors were invasive, and two-thirds were invasive ductal cancers. All the patients in the hormone therapy groups had estrogen and/or progesterone receptor-positive

tumors. The HER2 status did not differ significantly in the different groups. The distribution of the irradiated volumes among the 4 groups, together with other radiotherapy-related data, are presented in Table 1. The rate of locoregional radiotherapy, and as a consequence, the MLD and $V_{20\text{ Gy}}$ were significantly higher in the Taxane group ($p<0.001$) (Table 1). The proportion of past or present smokers was the highest in the Tamoxifen group ($p=0.052$). Radiation pneumonitis of grade I was found in 41.8% of the patients, and 5.8% had mild clinical symptoms. Radiation fibrosis of grade I developed in 30.4% of the patients; none of them had symptoms. The incidence of radiation pneumonitis or fibrosis did not exhibit significant variations during the study. The presence of early or late radiogenic lung damage was compared with the various patient- and radiotherapy-related characteristics (Tables 2 and 3).

	No change (n=191)	Pneumonitis of grade I			
		Symptomatic (n=19)	p vs. No change	Any (n=137)	p vs. No change
<i>Age (mean±SE, years)</i>	57.8±0.8	63.4±2.3	0.036	61.5±0.9	0.009
<i>Irradiated volume</i>					
<i>Chest wall</i>	66 (34.6%)	10 (52.6%)	0.086	47 (34.3%)	0.963
<i>Breast</i>	125 (65.4%)	9 (47.4%)		90 (65.7%)	
<i>Irradiation of the regional lymph nodes</i>					
<i>Yes</i>	63 (33.0%)	10 (52.6%)	0.189	63 (46.0%)	0.017
<i>No</i>	128 (67.0%)	9 (47.4%)		74 (54.0%)	
<i>MLD (Gy)</i>	10.2±0.3	12.7±1.1	0.019	11.7±0.4	0.011
<i>V_{20Gy} (%)</i>	20.1±0.8	25.7±2.7	0.024	23.4±0.8	0.017
<i>Present or past smokers</i>	78 (40.8%)	5 (26.3%)	0.232	51 (37.2%)	0.509
<i>Non-smokers</i>	113 (59.2%)	14 (73.7%)		86 (62.8%)	

Table 2 Associations of patient- and radiotherapy-related characteristics of the study population and the early radiation lung sequelae

	No change (n=218)	Fibrosis of grade I (n=95)	p
<i>Age (mean±SE, years)</i>	57.9±0.7	63.6±1.1	<0.001
<i>Irradiated volume</i>			
<i>Chest wall</i>	61 (28.0%)	46 (48.4%)	<0.001
<i>Breast</i>	157 (72.0%)	49 (51.6%)	
<i>Irradiation of the regional lymph nodes</i>			
<i>Yes</i>	65 (29.8%)	51 (53.7%)	<0.001
<i>No</i>	153 (70.2%)	44 (46.3%)	
<i>MLD (Gy)</i>	9.9±0.3	12.6±0.4	<0.001
<i>V_{20Gy} (%)</i>	19.4±0.7	25.4±1.0	<0.001
<i>Present or past smokers</i>	92 (42.2%)	32 (33.7%)	0.157
<i>Non-smokers</i>	126 (57.8%)	63 (66.3%)	

Table 3 Associations of patient- and radiotherapy-related characteristics of the study population and the late radiation lung sequelae

Highly significant associations were found between the presence of early or late radiogenic lung changes and the age of the patient, the MLD and the $V_{20\text{ Gy}}$. There was a weak negative correlation between the age and the MLD in the overall study population ($r=-0.143$, $p=0.009$). Nodal irradiation favored lung damage ($p=0.017$ at 3 months, and $p<0.001$ at 1 year after the radiotherapy). One year following the radiotherapy, fibrosis of grade I was more frequent when mastectomy had been performed ($p<0.001$) (Table 3), though this was probably a consequence of the higher frequency of supraclavicular and axillary irradiation after mastectomy than after tumor excision (49.6% vs. 32.6%, respectively, $p<0.003$). A past or present history of smoking did not influence the degree of radiogenic lung damage 3 months and 1 year after the radiotherapy (Tables 2 and 3). The incidence of pneumonitis of grade I or fibrosis of grade I did not differ in the 4 treatment groups, but most cases of symptomatic pneumonitis were observed in the Tamoxifen group ($p=0.076$) (Table 4).

	Pneumonitis of grade I, symptomatic (n=19)		Pneumonitis of grade I, any (n=328)		Fibrosis of grade I (n=313)	
	Incidence (%)	OR (95% CI, p)	Incidence (%)	OR (95% CI, p)	CT change (%)	OR (95% CI, p)
Control	4/90 (4.4%)	1.00	35/90 (38.9%)	1.00	22/86 (25.6%)	1.00
Taxane	2/79 (2.5%)	0.558 (0.099-3.134, 0.508)	27/79 (34.2%)	0.816 (0.435-1.531, 0.526)	18/70 (25.7%)	1.007 (0.489-2.047, 0.985)
Tamoxifen	9/77 (11.7%)	2.846 (0.840-9.638, 0.093)	39/77 (50.6%)	1.613 (0.871-2.985, 0.128)	31/76 (40.8%)	2.004 (1.029-3.902, 0.041)
Aromatase inhibitor	4/82 (4.9%)	1.103 (0.267-4.559, 0.893)	36/82 (43.9%)	1.23 (0.669-2.259, 0.505)	24/81 (29.6%)	1.225 (0.621-2.417, 0.559)
p	0.076		0.185		0.134	

Table 4 OR and 95% CI for pneumonitis and fibrosis of grade I associated with the various forms of systemic therapy

When the effect of the age of the patient on the radiogenic lung changes was analyzed in the different treatment groups, the patients with symptomatic pneumonitis in the Tamoxifen group proved to be significantly older than the patients without lung damage ($p=0.013$) (Fig. 6).

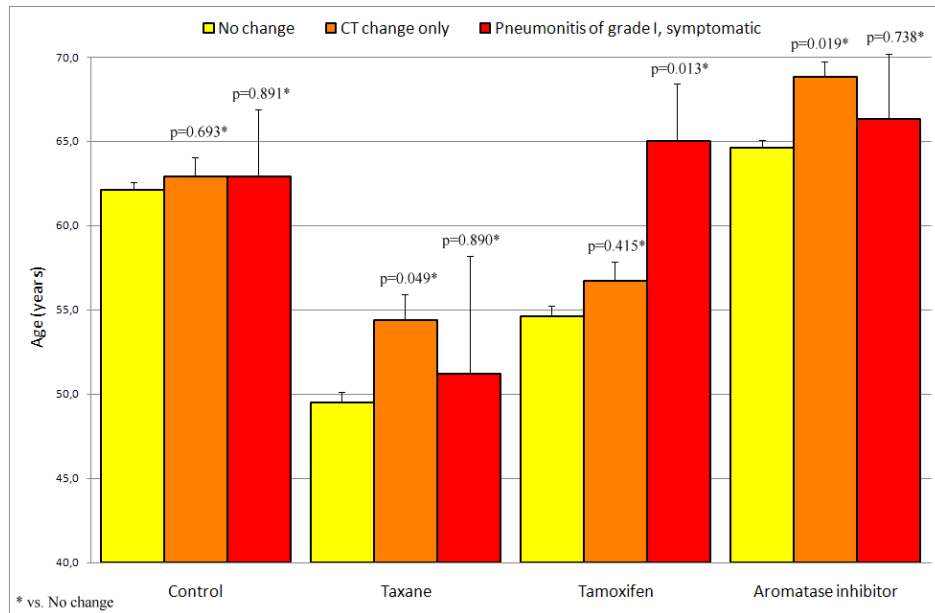


Figure 6 Associations of pneumonitis of grade I and age (mean±SE) with the various forms of systemic therapy

A significant association was found between the presence of pneumonitis of grade I and the presence of fibrosis of grade I ($p < 0.001$, McNemar test). The extents of the lung density changes depended on the presence and the severity of radiation pneumonitis or the development of fibrosis, 3 months or 1 year after the radiotherapy, respectively, but did not differ significantly as a function of the systemic therapy (Figs. 7 and 8).

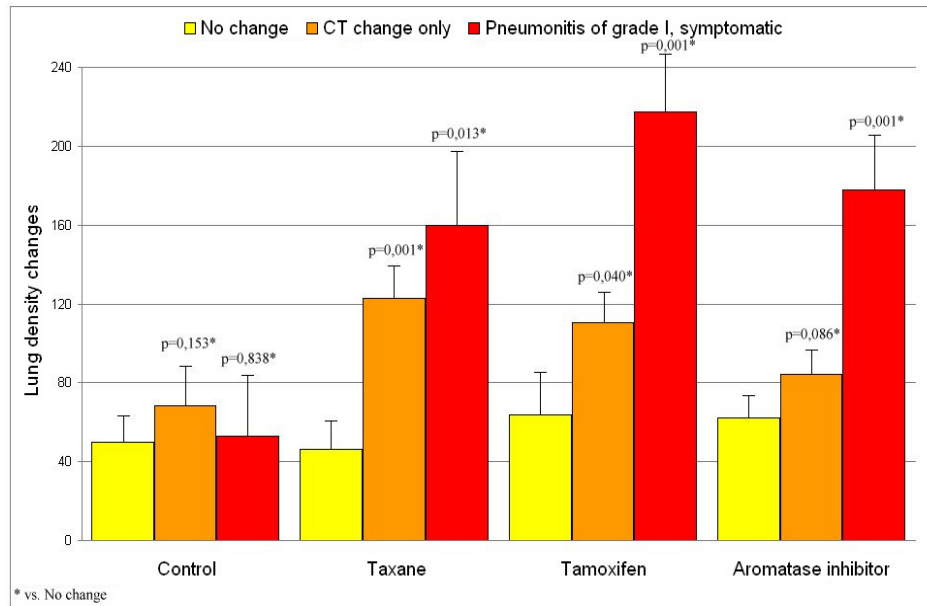


Figure 7 Associations of lung density changes (mean±SE) measured 3 months after radiotherapy at the level of the left heart ventricle (MDC_{LHV}) with occurrence and severity of radiation pneumonitis and the various forms of systemic therapy

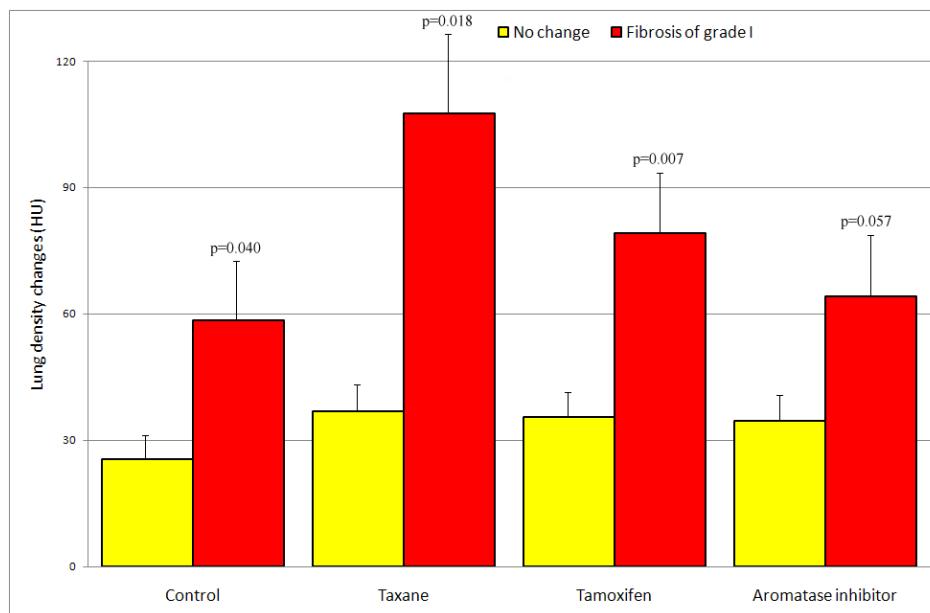


Figure 8 Associations of lung density changes (mean±SE) measured 1 year after radiotherapy at the level of the left heart ventricle (MDC_{LHV}) with the occurrence of radiation fibrosis and the various forms of systemic therapy

4.1.2. Univariate analysis

In order to estimate the risks of pneumonitis or fibrosis, the effects of the age of the patient, the MLD, and the different modes of systemic treatment were first studied in binary univariate logistic regression models. The risks of pneumonitis of grade I and fibrosis of grade I were increased 3 months and 1 year, respectively, after the radiotherapy, with OR=1.030 (95% CI: 1.009-1.051, $p=0.004$) and OR=1.054 (95% CI: 1.029-1.081, $p<0.001$), respectively, for every 1-year increase in the age of the patient. Significant positive associations were demonstrated between the risk of pneumonitis of grade I and the MLD (OR=1.080; 95% CI: 1.027-1.135, $p=0.003$) and between the risk of fibrosis of grade I and the MLD (OR=1.156; 95% CI: 1.091-1.224, $p<0.001$) for every 1.0-Gy increase. Significant associations were not found between the risks of early or late radiogenic lung damage and the addition of systemic therapy (Table 4).

4.1.3. Multivariate analysis

The joint effects of the age, the MLD, the systemic treatment and their interactions were examined in a multiple logistic regression model, using a stepwise algorithm. All three variables remained significant in the model (Table 5).

	Pneumonitis of grade I, symptomatic			Pneumonitis of grade I, any			Fibrosis of grade I		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age	1.041	0.991-1.094	0.106	1.035	1.011-1.061	0.005	1.074	1.042-1.107	0.001
MLD	1.126	1.009-1.256	0.033	1.113	1.049-1.181	0.001	1.207	1.124-1.295	0.001
Systemic treatment			0.064			0.080			0.010
Taxane	0.465	0.066-3.268	0.442	0.674	0.309-1.470	0.322	0.750	0.294-1.915	0.548
Tamoxifen	2.775	0.746-10.323	0.128	1.679	0.863-3.266	0.127	2.442	1.120-5.326	0.025
Aromatase inhibitor	0.804	0.188-3.435	0.768	0.955	0.504-1.806	0.887	0.765	0.359-1.632	0.488

Table 5 Multivariate analysis of the effects of age, the MLD and the systemic therapy on the early and late radiogenic lung sequelae

Whereas the risks of any radiation pneumonitis and that with symptoms and the administration of systemic therapy displayed non-significant trends ($p=0.080$ and $p=0.064$, respectively), the risk of fibrosis was significantly elevated by the administration of systemic therapy ($p=0.001$) or of tamoxifen ($p=0.025$). The joint effects of the age, the MLD and the systemic treatment on the risk of radiation fibrosis are illustrated in Fig. 9.

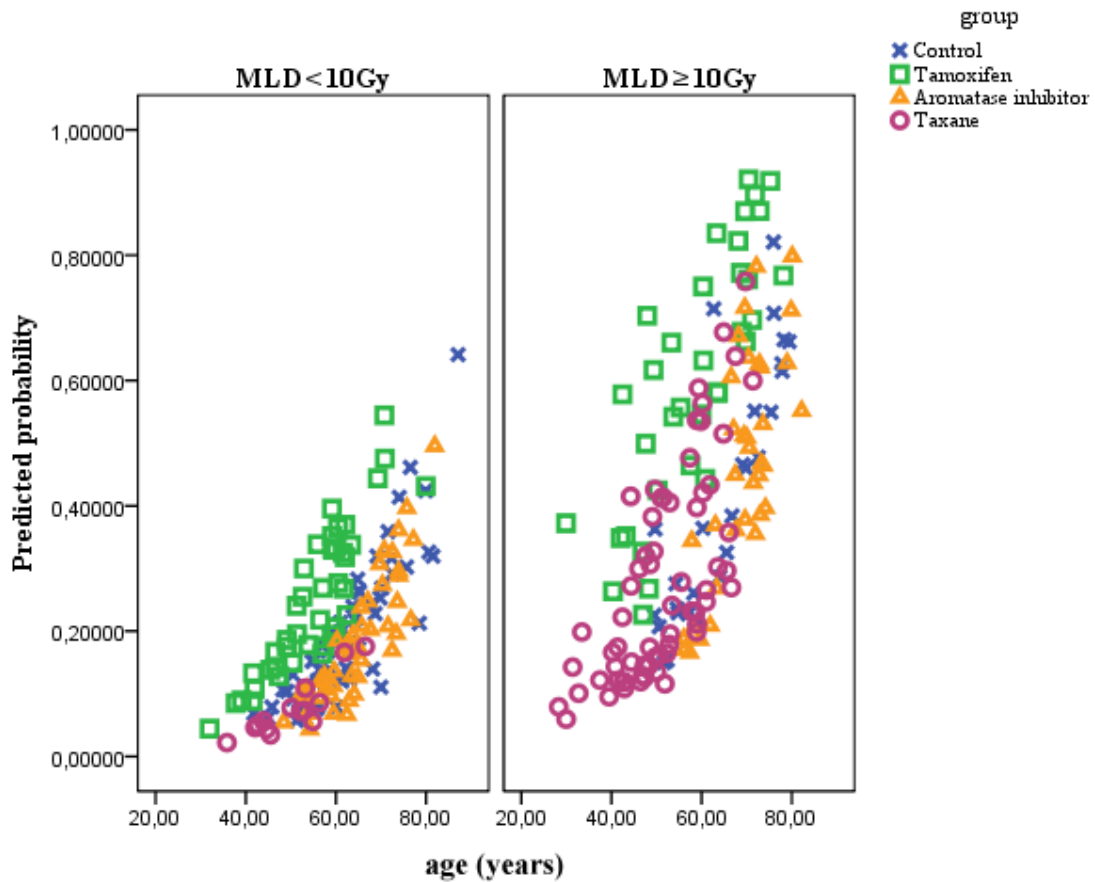


Figure 9 The risk of radiation fibrosis of grade I as indicated by the multivariate logistic regression model including the age of the patient, the radiation dose to the ipsilateral lung and the type of systemic treatment. Note that although in the model MLD was a continuous variable, in the graph for delineation, the median MLD value of 10 Gy was used as a threshold.

Only the interaction of the age and the MLD remained significant in the development of late CT abnormalities (OR=1.006; 95% CI: 1.000-1.013, $p=0.050$ with every 1-year increase in the age of the patient and every 1-Gy increase in the MLD). No interaction

was detected for the various types of systemic therapy and the dosimetric parameters, irrespective of whether the analysis extended to the entire population or only to an older age group.

4.2. The effects of individual positioning on the radiation exposure of the risk organs

4.2.1. General statistics

The first phase of the study and the second, feasibility phase involved 20 and 41 patients, respectively. The mean (\pm SD) age of the overall study population was 56.0 ± 9.6 (29.3-73.9), and that in the second phase was 56.6 ± 9.9 (29.3-73.6) years. Twenty-seven patients needed right-sided, and 34 underwent left-sided breast irradiation. The age, weight, waist, hip size and breast separation did not differ significantly between the patients randomized to radiotherapy in the prone or the supine position (Table 6).

	Age (years)	Weight (kg)	Height (cm)	BMI (kg/cm ²)	Waist size (cm)	Hip size (cm)	Breast separation (cm)
Supine n=21	59.1 \pm 9.3 (42.1-75.0)	71.6 \pm 12.4 (52.0-96.0)	162.1 \pm 7.7 (150-175)	27.2 \pm 3.9 (20.9-33.2)	93.3 \pm 14.4 (78-145)	107.4 \pm 12.1 (95-150)	21.1 \pm 2.7 (16.4-26.9)
Prone n=20	56.9 \pm 10.7 (30.7-72.4)	69.9 \pm 12.4 (50.0-102.0)	161.0 \pm 4.3 (152-168)	27.1 \pm 5.3 (17.7-38.9)	89.3 \pm 10.6 (69-108)	104.4 \pm 9.9 (87-124)	20.7 \pm 3.1 (14.2-26.9)
p	0.49	0.66	0.56	0.94	0.32	0.40	0.64

Table 6 Patient characteristics (mean \pm SD) among patients randomized to radiotherapy in the prone vs. the supine position

Tumor bed boost irradiation and systemic treatments did not differ significantly between the two groups.

4.2.2. Radiotherapy plans for the prone vs. the supine position

The radiotherapy plans were first analyzed in the overall population. The mean (\pm SD) percentage PTV covered by 47.5-53.5 Gy ($V_{95-107\%}$) in the prone vs. the supine position was $85.1 \pm 4.2\%$ and $89.2 \pm 2.2\%$, respectively ($p < 0.0001$). The dose homogeneity did not depend on the PTV or the breast separation. The irradiated volume of and the dose to the

ipsilateral lung determined in terms of the MLD and the V_{20Gy} were dramatically lower in the prone position than in the supine position (Table 7).

	Lung (n=61)		Heart (n=34)		
	MLD (Gy)	V_{20Gy} (%)	Mean dose (Gy)	V_{25Gy} (%)	V_{30Gy} (%)
Supine	7.45±2.62	14.3±5.4	3.51±2.33	4.7±4.6	4.1±4.3
Prone	2.02±1.23	3.3±2.5	3.18±1.31	3.6±2.5	3.0±2.2
p	<0.0001	<0.0001	0.413	0.171	0.152

Table 7 Radiation doses to the ipsilateral lung and the heart in the overall study population. The mean values±SD are shown.

No significant difference was detected in the mean dose to the heart and the volumes of the heart receiving at least 25 Gy or 30 Gy in 34 left-sided breast cancer patients according to their position during radiotherapy (Table 7). The first 20 pairs of treatment plans revealed significantly higher doses to the contralateral breast in the prone position than in the supine position. In the second phase of the study (n=41), as a consequence of the more complete displacement of the opposite breast due to the use of a new polyfoam wedge, there was no longer any significant difference (Table 8).

	First phase n=20		Second phase n=41		p for first vs. second phase	
	Mean dose (Gy)	V_{5Gy} (%)	Mean dose (Gy)	V_{5Gy} (%)	Mean dose	V_{5Gy}
Supine	0.85±0.47	2.7±2.0	0.61±0.73	1.7±2.8	0.096	0.073
Prone	1.26±0.78	4.5±3.4	0.74±0.44	2.2±2.0	0.00092	0.001
p for supine vs. prone	0.0038	0.0057	0.162	0.159		

Table 8 Radiation dose to the opposite breast in the 2 consecutive cohorts of the study

We hoped to identify those parameters related to the patient anatomy which indicate high lung doses if radiotherapy is given in the supine position, in order to select those patients who would benefit most from radiotherapy in the prone position. As regards the volume of the target breast, the breast separation and the CLD, only the CLD was significantly associated with the MLD ($r=0.843$, $p<0.0001$) and the $V_{20\text{Gy}}$ ($r=0.733$, $p<0.0001$).

4.2.3. Implementation of breast radiotherapy in the prone position

In the second phase of the study, the adherence to the study protocol, the repositioning accuracy and the early skin reactions were analyzed. The protocol was tolerated well by all the patients; only one patient treated in the prone position needed a 1-week break because of radiodermatitis. It was necessary to correct the location of the isocenter in the simulator or the position of the table during radiotherapy in 20.3% (61/301) and 20.3% (62/306) of all the checks in the prone and the supine position, respectively ($p=0.999$). The mean length of the displacement vector was 8.06 ± 4.66 (3.00–22.56) mm and 6.60 ± 3.05 (3.00–21.19) mm in the prone and supine position, respectively ($p=0.021$). The population random errors were 3.89 mm and 2.97 mm, while the population systematic errors were 0.86 mm and 0.82 mm, for the prone and the supine position, respectively. The random errors in the two groups are shown in Table 9.

	Mean \pm SE (mm)	Median (mm)
Supine	2.75 ± 0.27	2.58
Prone	3.46 ± 0.37	3.48
p	0.061	

Table 9 Random errors for repositioning in the prone and supine positions

A trend was detected for better overall repositioning accuracy in the supine position ($p=0.061$). We analyzed whether the repositioning accuracy changed from patient to patient during the study period. The individual random errors for repositioning in the prone position decreased with time, while no change was detected in the group randomized to radiotherapy in the supine position (Fig. 10).

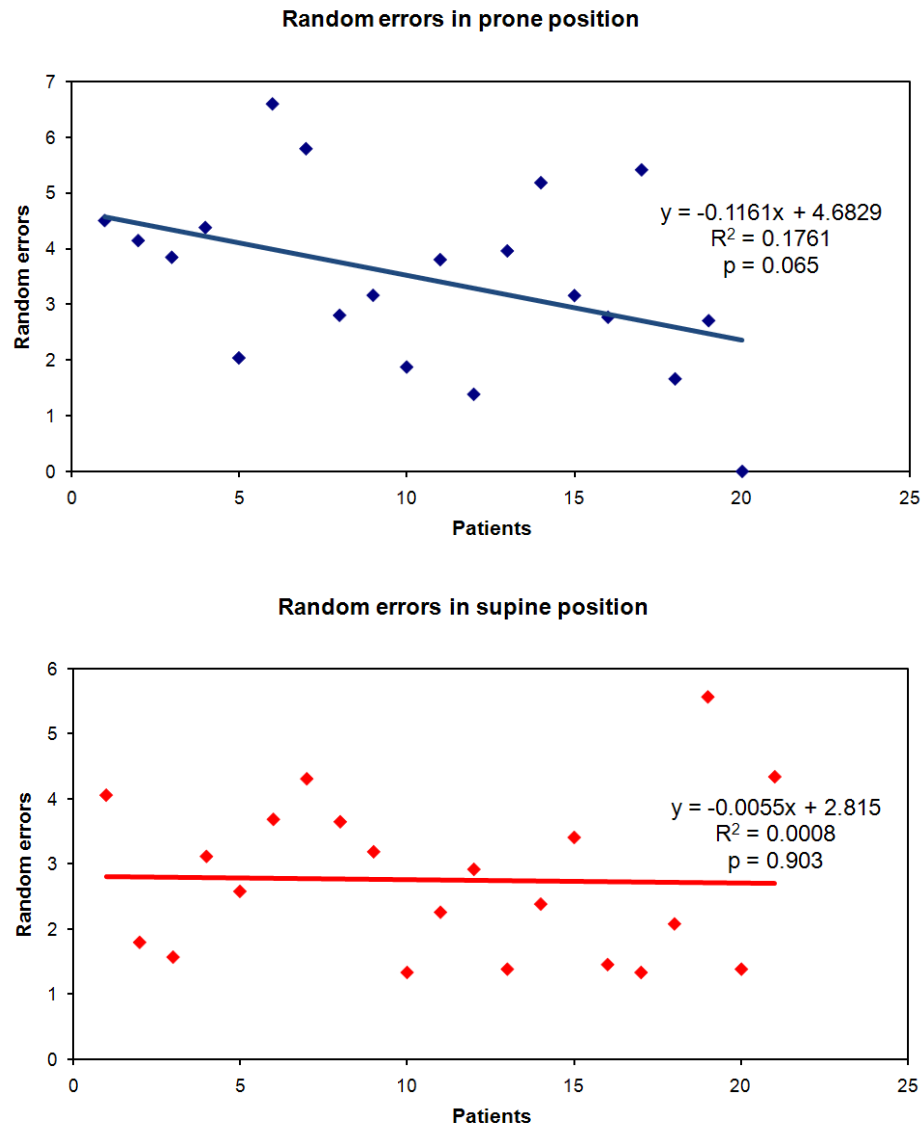


Figure 10 Random errors for repositioning among the patients who received radiotherapy prone and those received radiotherapy supine by sequence of enrolment in the study

The repositioning accuracy in the prone position, did not depend on any of the patient-related parameters. In the supine position, however, the repositioning accuracy was significantly related to lower weight ($p=0.01$), the BMI ($p=0.011$), the waist size ($p=0.039$), the volume of the ipsilateral breast ($p=0.007$) and the breast separation ($p=0.001$). Radiodermatitis of grade I developed in 55% and 38.1%, and radiodermatitis of grade II in 35% and 19.5% of the patients receiving radiotherapy in the prone or the

supine position, respectively ($p= 0.025$). Acute skin reactions were not related to dose homogeneity in the PTV or the random errors for repositioning, regarded as measures of systematic and random overdosage, respectively.

5. Discussion

5.1. The risk of early and late lung damage after conformal radiotherapy

Although about one-third of the patients had developed radiographic changes by 3 months and 1 year after the radiotherapy in our prospective study, only a minority suffered from symptoms that were easily managed, and none had respiratory problems 1 year after the radiotherapy. Thus, in accord with the literature data, we found that significant radiogenic lung sequelae after conformal radiotherapy in breast cancer were rare. The strongest risk predictor for radiation lung sequelae was the MLD and the age of the patient. Based on a complex set of clinical data on 328 breast cancer patients, our analysis revealed that the concomitant administration of tamoxifen with adjuvant radiotherapy independently increases the risk of radiation lung fibrosis, while the aromatase inhibitors and sequential taxane-based chemotherapy have no such effect. We believe that our findings with the advantages of conformal radiotherapy and individualized adjuvant systemic therapy, make a notable contribution to the clarification of the discrepancy that has long existed regarding the relation of systemic treatment and radiation lung damage, and indicates the need for the withdrawal of tamoxifen during adjuvant radiotherapy.

Tamoxifen has been widely applied for the treatment of breast cancer in the adjuvant setting, and its co-administration with adjuvant radiotherapy has been the subject of numerous studies (7, 8, 10, 12, 13, 16–18, 31). In some of them, the incidence of radiation lung complications did not differ when tamoxifen was or was not administered simultaneously with radiotherapy (7, 8, 10, 17, 18). The negative results might have been due to the retrospective nature of the analyses (10, 16), the underpowered study populations (8, 15, 18), the limitation of the study end-point to pneumonitis (8) or the low sensitivity of the method of follow-up (10, 17). In other studies, the incidence of radiogenic pulmonary fibrosis proved to be significantly higher in the patients treated with tamoxifen (12–14). The first such trial was that of Bentzen et al. (12): in a randomized study of 84 postmenopausal women, the risk of radiation fibrosis in the axillary and supraclavicular fields was doubled when tamoxifen was co-administered with

the radiotherapy. Koc et al. applied postoperative telecobalt irradiation in 111 patients, and observed that regular chest CTs revealed lung fibrosis rates of 35% when tamoxifen was administered during the radiotherapy vs. 13% when it was not (13). Huang et al. reported that tamoxifen therapy was an independent risk factor of radiation lung fibrosis when co-administered during electron-irradiation of the chest wall (OR= 3.35, $p= 0.03$) (14). These three studies did not involve the use of conformal radiotherapy, and could not include DVH data in the analysis. The strength of our study is that, besides confirming tamoxifen as a risk factor in the development of radiogenic lung fibrosis, it investigated the role of systemic therapy independently of the simultaneous effects of dosimetric factors and age. These parameters can easily be taken into consideration when deciding about the radiotherapy.

The use of third-generation aromatase inhibitors is currently the standard endocrine therapy of postmenopausal women with hormone-dependent breast cancer (32). For this reason, we set out to test the effects of anastrozole and letrozole administered in conjunction with radiotherapy. Although estrogen deprivation could in theory exert a disadvantageous effect on the post-irradiation tissue remodelling, no change was observed in the risk of radiogenic lung sequelae. Our results accord with those of Azria and Ozsahin, who found no association between the concomitant administration of letrozole with radiotherapy and the development of subcutaneous fibrosis (33, 34). As far as we are aware, ours is the first well-powered study that has specifically pointed to lung complications and the use of aromatase inhibitors in the clinical radiotherapy setting.

The findings regarding the risk of radiation pneumonitis following chemotherapy are controversial. Radiation lung sequelae were found to be more frequent in breast cancer patients who received chemotherapy in some studies (13, 15), whereas in others no difference was seen (10, 17). Early reports on the co-administration of paclitaxel with adjuvant radiotherapy suggested an increased risk of lung sequelae (35, 36), whereas Yu et al. found equally low incidences of radiation pneumonitis and no difference between the two groups (5% vs 4.5%) (37). In our study, the provision of chemotherapy involving paclitaxel or docetaxel was not associated with a higher risk of radiation pulmonary complications. In fact, despite the significantly higher irradiated lung volumes, the incidence of pulmonary toxicity was negligible. This finding can be explained in terms of the significantly younger age in the Taxane group, and is consistent with our results demonstrating the greatest influence of the age on lung complications (9). Tamoxifen

group, those patients who developed radiation pneumonitis were significantly older than those who did not (Fig. 6). The question arose as to whether tamoxifen treatment is in synergy with age, but our analysis did not support this. In the Control and Aromatase inhibitor groups, the radiogenic lung changes were not related to age, probably because of the lack of a similarly broad range of age as in the Tamoxifen group.

We performed lung density measurements with the aim of a quantitative assessment of the effects of systemic therapy on radiogenic abnormalities. MDCs well correlated with the occurrence of radiation pneumonitis or fibrosis. The lack of association between the MDCs and medical therapy may primarily be a result of the method applied, i.e. the measurement in certain predetermined lung areas and the exclusion of inflammatory or fibrotic changes from the field of interest during the procedure. Thus, the determination of MDCs provides complementary, quantitative information about prespecified lung areas, instead of detecting striking visible changes in the entire irradiated lung volume.

5.2. The effects of individual positioning on the radiation exposure of the risk organs

We evaluated our initial experience regarding the dosimetry and feasibility of conformal breast radiotherapy in the prone position, and identified its place in everyday practice. Our results indicate that its primary advantage is the significantly reduced radiation exposure of the ipsilateral lung. Special practice in and attention to accurate repositioning are needed if the prone position is applied, and the dose inhomogeneity and acute skin reactions may be slightly increased.

There have been few studies on prone breast radiotherapy. Some of them focused on the dose distribution (20, 21, 23, 38), and others on clinical implementation (25-27, 39), and only one study dealt with both dosimetric aspects and feasibility (24). The present study is the first randomized clinical trial to compare breast radiotherapy in the prone vs. the supine position.

Utilization of the prone position during breast radiotherapy raises special considerations because of the altered shape, motion and position of the organs present in the region. The altered shape of the target breast hanging down across the aperture of the positioning device results in a different dose distribution relative to that in the supine position. Improved dose uniformity, and especially the avoidance of an overdosage within the PTV, have been associated with a better cosmetic outcome (40, 41). A higher dose inhomogeneity is related to larger breasts if conventional tangent beams are used (40).

Buijsen et al. (23) compared prone and supine breast irradiation in 10 patients with pendulous breasts, and concluded that the dose homogeneity was better in the prone than in the supine position. In fact, this was based on a comparison of the PTV overdosed ($V_{105\%}$ and $V_{107\%}$) in the supine vs. the prone position, while the significantly lower mean dose and PTV coverage representing an underdosage were neglected. Similarly, larger volumes receiving >52.5 Gy within the PTV were found in the supine than in the prone position, but no other information on dose distribution was reported in another study (20). We examined $V_{95-107\%}$ as a measure of dose homogeneity within the PTV, according to ICRU Report 62, and found that the dose distribution was significantly more uniform in the supine position, regardless of the size or shape of the target breast. None of the radiotherapy plans indicated measurable volumes receiving >53.5 Gy. Our dose prescription strategy was different from those of Buijsen et al. (23), and Griem et al. (20). A mean dose of 50 Gy was prescribed to the entire PTV, provided that the dose range is between 45-55 Gy in at least 95% of the PTV, instead of specifying a dose to a dose prescription point. We believe that our approach reliably represents the dose homogeneity within the PTV. Despite the use of in-field segments, we observed hot spots at the top and the bottom of the target breast in the prone position, which is consistent with the experience of Mahe et al. (24).

Because of the different shape of the chest wall when the patient is positioned prone, the lung volume included in the tangent fields is considerably less. All authors agree that the lung doses are dramatically reduced if breast radiotherapy is performed with the patient prone (19-23). The beneficial effect of prone positioning on the protection of the ipsilateral lung is further enhanced if the almost absent intrafractional motion of the chest wall is taken into account for the calculation of safety margins around the CTV (39, 42, 43).

When left-sided irradiation is performed, the irradiated volume of the heart is not reduced, despite the fact that less intrathoracic volume is exposed to radiation in the prone than in the supine position. Reports on heart doses, however, are not concordant. Some studies suggest a reduction in heart doses as a result of prone positioning, but do not provide direct comparisons with supine positioning (19, 22). Others are consistent with our results in showing no significant difference in the doses to the heart as a function of the treatment position (20, 21, 23). This finding may be accepted if the change in position of the heart by treatment position is taken into consideration. In fact, the prone position causes an

anterior displacement of the heart within the thorax by 19 mm on average, as demonstrated by CT and MRI measurements in breast cancer patients receiving radiotherapy (44).

Since breast radiotherapy increases the risk of the late development of contralateral breast cancer by 18-34%, special attention is needed for the protection of the opposite breast during radiotherapy (45). Although some studies allude to the radiation dose to the opposite breast in the prone position, detailed dose volume histogram data have not been provided (19, 20).

The largest prospective phase I-II study on prone breast irradiation is that of Formenti et al. (22). Accelerated whole breast radiotherapy was feasible in 90 patients, with high set-up reproducibility, although numerical data were not provided. In another feasibility study (24), prolonged adequate immobilization could not be achieved in 3 of 35 patients with large pendulous breasts in the prone position. In one retrospective study (25), 5% of the patients during prone breast radiotherapy complained of chest wall or rib pain, and 2 of 248 patients suffered a rib fracture (25), as did 1 of 35 in the previous study (24). All our patients considered the prone radiotherapy convenient, and completed the course of radiotherapy. We believe, that the comfortable positioning system in use, was essential to achieve such good adherence to the protocol. It is our view that repositioning accuracy is a key condition for radiotherapy, especially if inverse or forward intensity modulation is applied (42, 43). During simulation in 308 patients with various cancer sites, Schüller et al. (46) found that the repositioning accuracy was better in the entire patient population if positioning aids or mask fixation were used, but did not differ by prone or supine positioning. Breast irradiation was performed in the supine position for 64 patients, without mask fixation. Of the various tumor sites, the breast exhibited the poorest repositioning accuracy. Displacement was carried out in 27 patients (42.2%), and in many cases exceeded 1 cm. In another study of 25 breast cancer patients irradiated in the supine position (47), the isocenter displacement on simulation was on average 5.7 mm. Morrow et al. (39) studied the interfractional error in repositioning in 15 patients, and recommended image guidance during prone breast radiotherapy because of the need for frequent and large displacements. In accord with our results, they observed no relation between the breast size and the repositioning accuracy. Interestingly, however, we found that the repositioning accuracy in the supine position is significantly worse in obese patients. To the best of our knowledge, no such data have been published previously. If

confirmed, they indicate that increased attention must be paid to the position of overweight patients during breast radiotherapy. We believe that the relatively good repositioning accuracy in our study, was related to the comfortable positioning device used for both the prone and the supine position, and to the mask fixation used in the supine position. The repositioning accuracy in the prone position improved over time, indicating the need for experience and expertise if the method is newly introduced. Furthermore, our study warrants the development of mask fixation in the prone position, which would reduce the set-up uncertainty.

In other publications (24, 25), acute skin reactions after breast radiotherapy in the prone position were reported in similar incidences as among our patients. Mahe et al. (24) found that acute skin reactions were most frequent at the top and the bottom of the fields, in accordance with the high dose regions. In our study, radiodermatitis in the prone position was not related to the size of the breast or the dose-inhomogeneity in it.

Merchant and McCormick (19) recommend breast radiotherapy in the prone position if that in the supine position is likely to result in unacceptable dose inhomogeneity or significant doses to normal tissues. We hoped to identify those patients who would benefit most from the prone position during breast radiotherapy. Since we could not detect any advantage of prone radiotherapy other than the absence of radiation exposure of the lung, we set out to identify those patient-related parameters that are associated with a higher lung dose if the patient is irradiated in a supine position. Consideration of the volume of the breast, the breast separation and the CLD as measures of the shape of the PTV indicated that only the CLD was related to the dose to the ipsilateral lung. Thus, we recommend monitoring of the CLD as a primary measure for an indication for prone radiotherapy. Moreover, since the risk of early and late radiation lung sequelae is strongly related to the age of the patient (9) and the presence of lung diseases, and possibly also to certain systemic therapies, these factors should be taken into account when a decision is made concerning the position during breast radiotherapy.

6. Summary, conclusions

6.1. The strongest risk factor for early radiogenic lung damage is the age of the patient. The volume of the irradiated lung and the dose to it are also significant risk predictors, which exert synergistic effects with age. Hence, primarily these parameters should be censored when adjuvant radiotherapy is delivered to early breast cancer patients. The concomitant administration of tamoxifen with adjuvant radiotherapy independently increases the risk of radiation lung fibrosis, while the aromatase inhibitors and sequential taxane-based chemotherapy exhibit no such effect. Our results suggest that tamoxifen should not be administered during radiotherapy.

6.2. Conformal breast radiotherapy is feasible in the prone position. Its primary advantage is the substantially lower radiation dose to the ipsilateral lung. The higher dose inhomogeneity and the enhanced rate of grade 1-2 skin toxicity, however, may be concerns. We recommend monitoring of the CLD as a primary measure for an indication for prone radiotherapy. Special practice in and attention to accurate repositioning are needed if the prone position is applied.

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Appendix