Radiation Induced Lung Reactions in Breast Cancer Therapy

Modulating Factors and Consequential Effects

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Background and Purpose: Radiologic reactions in lung, usually subclinical, are a frequent side effect of radiotherapy for breast cancer. This study was initiated to identify effects of age and tamoxifen on radiation pneumonitis and consequent fibrosis.

Patients and Methods: Retrospectively, 451 patients irradiated postoperatively between 1992 and 1995 at the Department of Radiotherapy of Carl-Thiem-Klinikum (Cottbus, Germany) were analyzed. The median age was 58 years. After mastectomy (n = 296), 25 × 2.0 Gy were applied; breast-conserving surgery (n = 155) was followed by 30 × 2.0 Gy. In 221 patients, adjuvant tamoxifen was given. Follow-up included thorax radiography after 15 weeks and 1 year. In patients with reversible observations in standard chest radiography from 15 weeks to 1 year, CT or high-resolution (HR-)CT scans were analyzed after 4–7 years.

Results: Clinical symptoms of pneumonitis were seen in 25 patients (5.5%), all with radiologic changes. Early radiologic changes were detected in 134 patients (29.7%). Age (> 58 years; p = 0.0127) and tamoxifen (p = 0.0001) were found as significant parameters of early pneumopathy. Late radiologic changes were seen in 94/425 patients (22.1%), all after a positive early reaction (p = 0.001).

Conclusion: A low incidence of clinically symptomatic pneumonitis was observed, while the vast majority of patients presented with early radiologic changes. Higher age and tamoxifen treatment significantly increased the incidence of early pneumopathy. Local fibrotic responses must be expected in all patients with early reactions, indicating a strong consequential component of the late reaction.

Key Words: Radiotherapy · Lung · Pneumonitis · Fibrosis · Breast cancer · Tamoxifen · Age

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Strahlenreaktionen der Lunge bei der Therapie von Mammakarzinomen. Einflussfaktoren und konsekutive Effekte

Hintergrund und Ziel: Radiologische Veränderungen in der Lunge, üblicherweise ohne klinische Konsequenzen, sind eine häufige Nebenwirkung der Strahlentherapie von Mammakarzinomen. In der vorliegenden Studie sollte der Einfluss des Alters und der Tamoxifenbehandlung auf die strahleninduzierte Pneumonitis und die darauf folgende Fibrose untersucht werden.

Patienten und Methodik: In die retrospektive Analyse wurden 451 Patientinnen einbezogen, die zwischen 1992 und 1995 in der Klinik für Strahlentherapie des Carl-Thiem-Klinikums Cottbus eine postoperative Strahlentherapie erhalten hatten. Das mediane Alter betrug 58 Jahre. Nach Mastektomie (n = 296) wurden 25 × 2,0 Gy appliziert, nach brusterhaltender Operation (n = 155) 30 × 2,0 Gy. Bei 221 Patientinnen wurde adjuvant mit Tamoxifen behandelt. Die Nachuntersuchung beinhaltete die Auswertung von Röntgenaufnahmen des Thorax nach 15 Wochen und 1 Jahr. Bei Patientinnen mit reversiblen Veränderungen in der Standard-Thoraxaufnahme zwischen 15 Wochen und 1 Jahr wurden CT oder hochauflösende (HR-)CT-Untersuchungen zwischen 4 und 7 Jahren ausgewertet.

Ergebnisse: Klinische Symptome einer Pneumonitis wurden bei 25 Patientinnen (5,5%) beobachtet, die alle auch radiologische Veränderungen zeigten. Frühe radiologische Zeichen einer Pneumopathie wurden bei 134 Patientinnen (29,7%) gefunden. Alter (> 58 Jahre; p = 0,0127) und Tamoxifen (p = 0,0001) stellten sich als signifikante Einflussfaktoren für die frühe Pneumopathie dar. Späte radiologische Veränderungen zeigten sich bei 94/425 Patientinnen (22,1%), die alle auch frühe Veränderungen aufgewiesen hatten (p = 0,001).

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Schlussfolgerung: Die Inzidenz klinisch symptomatischer Pneumonitiden im untersuchten Patientengut war niedrig, während die große Mehrheit frühe radiologische Veränderungen zeigte. Mit höherem Alter und adjuvanter Tamoxifenbehandlung stieg die Inzidenz der frühen Pneumopathie signifikant an. Lokale fibrotische Veränderungen wurden bei allen Patientinnen mit frühen Reaktionen beobachtet, was auf eine starke konsekutive Komponente der Spätreaktion hinweist.

Schlüsselwörter: Strahlentherapie · Lunge · Pneumonitis · Fibrose · Mammakarzinom · Tamoxifen · Alter

Introduction

Documentation of side effects is a major prerequisite for quality management in the treatment of malignant tumors. With increasing cure rates and survival times, based on improved therapy approaches and techniques, the risk for the development of chronic treatment sequelae increases accordingly. This has to be considered for the design of treatment protocols.

Normal lung tissue is inevidently included in radiotherapy of breast cancer. This can result in the development of radiation pneumopathy, which, however, remains asymptomatic in the vast majority of patients. Analysis of lung reactions in this patient population can serve two purposes: first, it can be used as a model for radiobiological studies of normal lung tissue, not compromised by tumor burden and tumor response to treatment, in contrast e.g., to patients with bronchial carcinoma. Second, the effect of additional, e.g., hormonal treatment on lung reactions to radiation exposure can be studied.

Assessment of radiation-induced pneumopathy can be based on a variety of endpoints. Radiologic endpoints, from examinations with conventional thorax radiography, computed tomography (CT) or high-resolution (HR-)CT, are the dominant parameter; less frequently, clinical parameters are assessed. However, it has to be noted that the assessment of local morphological changes within the treatment volume does not necessarily reflect the clinical consequences [11]. The latter are stringently dependent on the residual functional lung volume, which may clinically completely compensate for impaired function in a subvolume.

The present, retrospective analysis was initiated to quantitate frequency and time course of radiation pneumopathy in patients treated by radiotherapy for breast cancer in adjuvant protocols. A total of 451 patients, treated postoperatively between 1992 and 1995 at the Department of Radiotherapy of Carl-Thiem-Klinikum in Cottbus, Germany, were analyzed. Endpoints comprised clinical and radiologic criteria. Moreover, effects of patients' age and additional hormonal treatment (tamoxifen) on the risk for radiation pneumopathy were analyzed.

Patients and Methods

Patients' characteristics

Files of patients receiving postoperative radiotherapy for breast cancer at the Department for Radiotherapy of Carl-Thiem-Klinikum in Cottbus, Germany, from 1992 to 1995 were reviewed. This cohort was chosen because of the highly uniform treatment technique applied over this time period. From 645 files, 194 patients with adjuvant chemotherapy, incomplete radiotherapy or preexisting pneumopathy were excluded. Chemotherapy was defined as an exclusion criterion because it might add – in an unknown manner – to the pulmonary toxicity of the treatment, and the present study was focused on radiation effects proper. Hence, a total of 451 patients were available for this retrospective analysis. Surgery was performed as breast conserving therapy (BCT) or as mastectomy (ME) in 155 patients (34.4%) and 296 patients (65.6%), respectively. Three patients were irradiated after bilateral ME.

Of the ME patients, > 80% had pT1–pT2 tumors according to UICC 1987; > 44% were pN0. Of the BCT patients, > 99% were pTIS–pT2, and > 76% were pN0. The median age at the onset of radiotherapy was 61 years (range 26–83 years) in the ME group, and 57 years (range 20–79 years) in the BCT group. Tamoxifen (usually 30 mg/d) was administered to a total of 221 patients, 171/296 (57.7%) in the ME group, and 50/155 (32.2%) in the BCT group.

Only standard follow-up procedures were applied, and hence no ethical approval was required. All procedures were in accordance with the Helsinki Declaration in its revised version of 1983.

Radiotherapy

Radiotherapy commenced at 5–6 weeks after surgery to allow for complete wound healing. Inpatients received six, outpatients five daily irradiations per week. CT–based, two-dimensional treatment planning was applied. A linear accelerator "Neptun 10p" (Institute of Nuclear Studies, Swerk, Poland) was used with 9-MeV photons and 8- to 10-MeV electrons.

The treatment technique was adjusted to the type of surgery. In the ME group, irradiation of the axillary, supraclavicular and parasternal lymphatics was included as well as of the thoracic wall according to the strategy of the department in the time period under investigation. A four-field technique was applied, with oblique anterior posterior fields (fields 1 and 2) to the axilla and supraclavicular region, a parasternal field (field 3), and an electron field (field 4) adjusted to the size of the scar region at the thoracic wall. Doses were 25 × 2.0 Gy in fields 1 and 2 (normalized to the center of the thorax), 25 × 1.8 Gy in field 3 (normalized to 2 cm tissue depth), and 20 × 2.0 Gy in field 4.

Fields 1 and 2 resulted in a homogeneous exposure of apical and lateral parts of the lung with 25 × 2.0 Gy, with the volume exposed depending on the patient's anatomy.

In patients with BCT and pNx and pN1–2 (group BCT1), the breast and ipsilateral axilla were included in the treatment volume (n = 131). In cases with pN0 (group BCT2, n = 24), irradiation of the breast alone was administered. The patients received 30 × 2.0 Gy normalized to the center of the mamma, resulting in an 80% isodose of 30 × 1.6 Gy to breast and axilla (and the lung volume exposed). No boost irradiation was administered. Photon irradiation was performed through tangential fields.

Follow-Up

All patients received a clinical examination and standard chest radiography 15 weeks after the end of irradiation in the Department of Radiotherapy. After 1 year, standard chest radiographs were requested from the respective general practitioners or radiologists. For this follow-up time point, a total of 346 radiographs were available, which were reexamined by specialists for radiotherapy or radiology at Carl-Thiem-Klinikum in Cottbus.

Of the patients with positive radiologic diagnosis at 15 weeks, 31 were negative in standard chest radiography at 1 year. These were recalled for further follow-up in 1999 (4–7 year after radiotherapy), when seven of the patients had deceased, and three did not comply. From four patients, earlier CT scans were available. Of the remaining 17 patients, HR-CT of the irradiated region (1.5 mm sections in 8-mm intervals) was performed.

Classification of Radiation Pneumopathy

Clinical symptoms of radiation pneumopathy were defined as dry cough, cough with sputum, increased body temperature, dyspnea and respiration-related thoracic pain. These symptoms reflect the grading according to RTOG/EORTC [28, 29].

Radiologic signs of pneumopathy were defined in more detail than in the RTOG/EORTC or LENT/SOMA classification. In standard chest radiography *at 15 weeks* pneumonitis was defined as increased density, hazy opacity, strand-like densities or an onset of shrinkage. *At 1 year*, dense strand-like residues, fibrotic strands and volumes, and mediastinal dislocations [30] were used as the lead symptoms.

CT-based diagnosis of fibrosis was made according to accepted criteria, i.e., thickened interlobular septae, subpleural strands, and fibrous intraparenchymal strands.

Statistical Analyses

All statistical procedures were performed with the Statistical Analysis System, SAS, release 8.02 (SAS Institute Inc, Cary, NC, USA). Multivariate analyses of variance were done with the general linear models (GLM) procedure of SAS [24], for the influence of age and tamoxifen treatment on pneumonitis (at 15 weeks) and the influence of age, tamoxifen and pneumonitis on fibrosis at 1 year or later. The number of fields was not included in the analysis, as this was a highly constant parameter within the individual treatment groups.

Results

The incidence of clinical symptoms and radiologic changes at 15 weeks and 1 year after radiotherapy is illustrated in Figure 1.

Clinical Symptoms

Clinical symptoms of pneumonitis were observed in 25/451 patients (5.5%). Of these, 21 were in the ME group (21/296 [7.1%]), and four in group BCT1 (4/155 [3.1%]). None of the patients in group BCT2 (local irradiation of the breast alone) developed clinical symptoms of pneumonitis (Figure 1).

In all patients, first clinical symptoms of pneumonitis developed before the first follow-up examination at 15 weeks, i.e., at 6 weeks in one case and at 7–8 weeks after the end of radiotherapy in all other patients. All symptomatic patients showed radiologic changes at 15 weeks.

Radiologic Changes at 15 Weeks

In the total population of patients, the incidence of radiologic pneumopathy at 15 weeks was 134/451 (29.7%). In the ME group, the incidence was 109/296 (36.9%), in group BET1 24/131 (18.3%), and in group BET2 1/24 (4.2%; Figure 1). Patients who were younger than the median age of 58 years developed pneumopathy in 21.7%, while the incidence in older patients was 37.8% ($p_{univar} = 0.0002$).

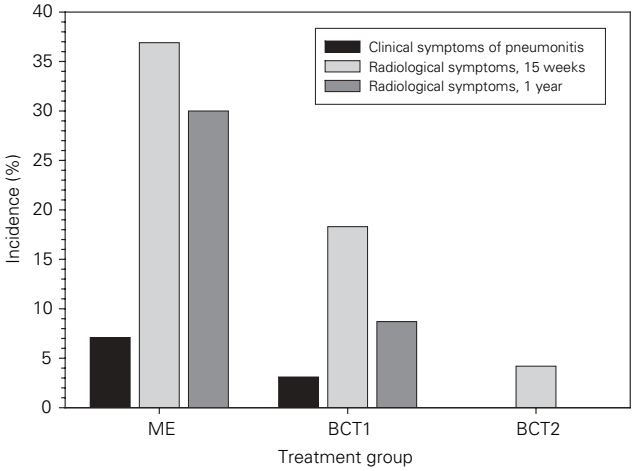

Figure 1. Incidence of clinical symptoms, radiologic symptoms at 15 weeks and at 1 year after radiotherapy. The patients received postoperative radiotherapy after mastectomy (ME, n = 296), or breast-conserving therapy (BCT), in the latter group locoregional (BCT1, n = 131) or local radiotherapy (BCT2, n = 24).

Abbildung 1. Inzidenz klinischer (schwarz) und radiologischer Zeichen (hellgrau) der Pneumopathie 15 Wochen sowie radiologischer Zeichen (dunkelgrau) 1 Jahr nach Strahlentherapie. Die Patientinnen erhielten eine postoperative Strahlentherapie nach Mastektomie (ME, n = 296) oder nach brusterhaltender Therapie (BCT) eine lokoregionäre (BCT1, n = 131) oder lokale Bestrahlung (BCT2, n = 24).

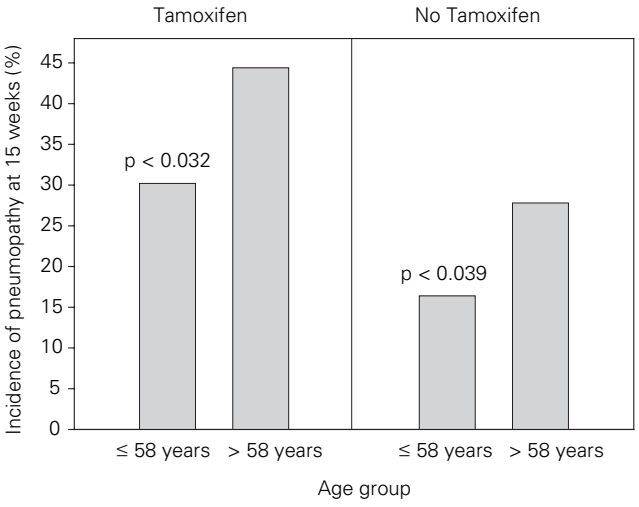

Figure 2. Incidence of early pneumopathy, at 15 weeks after the end of radiotherapy, in patients with (left panel, n = 221) or without (right panel, n = 230) administration of tamoxifen. The incidence is shown for patients younger or older than the median age of the entire population (58 years).

Abbildung 2. Inzidenz der frühen Pneumopathie, 15 Wochen nach Ende der Strahlentherapie, bei Patientinnen mit (linke Abbildung, n = 221) oder ohne (rechte Abbildung, n = 230) Tamoxifengabe. Die Häufigkeiten sind für Patientinnen dargestellt, deren Alter bei Therapie unter oder über dem Median der Gesamtpopulation von 58 Jahren lag.

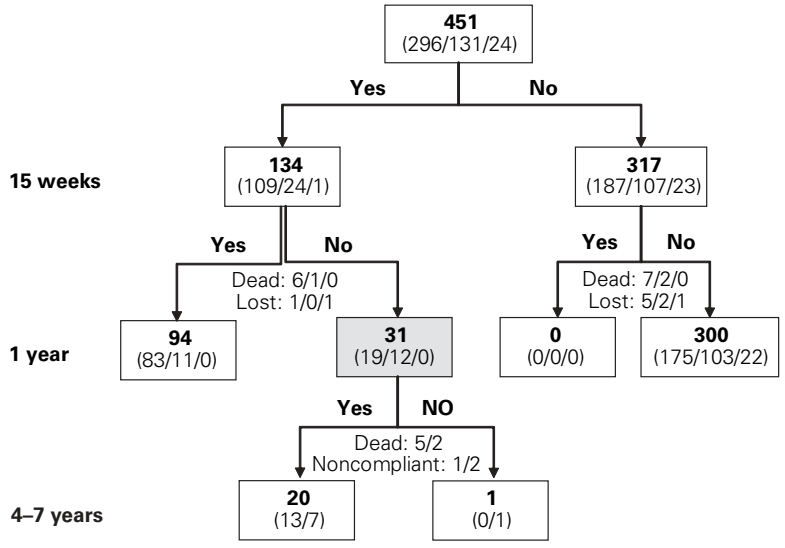

Figure 3. Numbers of patients with ("Yes") or without ("No") radiographic changes in the irradiated lung volume at 15 weeks or at 1 year after radiotherapy. In patients with a reversion of the response from 15 weeks to 1 year (shaded group), a CT or HR-CT analysis was added between 4–7 years after radiotherapy. Numbers in parentheses reflect the numbers of the individual treatment groups (ME/BCT1/BCT2).

Abbildung 3. Anzahl der Patientinnen mit („Yes") oder ohne („No") radiologische Veränderungen im bestrahlten Lungenvolumen 15 Wochen oder 1 Jahr nach Strahlentherapie. Bei Patientinnen mit positiven Reaktionen nach 15 Wochen, bei denen nach 1 Jahr keine Veränderungen festgestellt wurden (schattiert), wurde nach 4–7 Jahren eine weitere CT oder HR-CT ausgewertet. Die Zahlen in Klammern geben die Zahlen für die individuellen Behandlungsgruppen, d.h. ME/BCT1/BCT2, an.

In patients with tamoxifen treatment (n = 221), 86 developed pneumopathy (38.9%), with 30.2% in patients ≤ 58 years, and 44.4% in older patients (Figure 2), in contrast to 48/230 (20.9%; $p_{univar} = 0.0065$) in the group without tamoxifen, with 16.4% in patients ≤ 58 years, and 27.8% in older patients (Figure 2). Multivariate analysis revealed a significant effect of age (p = 0.0127) and tamoxifen treatment (p = 0.001). The significances were maintained when the surgical groups were included in the analysis, with $p_{age} = 0.0399$, and $p_{tamoxifen} = 0.014$.

Radiologic Changes at 1 Year and at 4–7 Years

Figure 3 summarizes the patient numbers at the individual time points and in the individual groups.

In the ME group, 277 patients were available for analysis at 1 years; 13 patients had died, and six were lost to follow-up. Radiologic fibrosis was found in 83 patients (30.0%) of this group, all of whom had presented with radiologic signs at 15 weeks.

In the BCT1 group, 126 patients could be analyzed at 1 year; two were lost to follow-up, and three had died. In eleven patients (8.7%), a positive radiologic response was found. Of the patients in the BCT2 group, two were lost to follow-up, one of which was the patient with pneumopathy at 15 weeks. Of the remaining 22 patients, none showed fibrotic changes.

In total, 94/134 early pneumopathies (75%) had progressed to fibrosis after 1 year. Of the remaining 31, nine were not included in the follow-up. Of the 317 patients without early pneumopathy, 17 were not available for follow-up, and 300 had no pneumopathy at 1 year (Figure 4).

Multivariate analysis revealed a significant effect of pneumopathy at 15 weeks (p < 0.0001), while age (p = 0.1245) and tamoxifen treatment (p = 0.2242) were not identified as significant sources. Moreover, no significant difference between treatment groups was observed for late fibrosis (p = 0.0942).

Patients with pneumopathy at 15 weeks with no radiologic (X-ray) changes at 1 year were subjected to analyses of CT or HR-CT scans at 4–7 years after radiotherapy.

In the 19 patients of the ME group, five had died in between, one patient was noncompliant. Two of the remaining 13 patients had external CT scans, which showed significant fibrotic changes at the same localization like 15 weeks after irradiation. In all of the other patients, fibrotic changes were observed in HR-CT scans, which included the volumes where changes at 15 weeks were found.

In group BET1, 8/12 patients were available for further examinations, two had died, and two did not want further diagnostics. In 2/8 patients,

external CT scans had revealed fibrotic changes, and similar changes were found in five HR-CTs of the remaining patients. Only in one patient, no changes were found.

Discussion

Radiation sequelae in normal lung tissue are a major side effect in the treatment of lung tumors. However, radiobiological studies in these patients are usually compromised by an impact of tumor burden and tumor response to therapy on the normal tissue reaction proper. Another instance, where lung reactions are frequently seen, although in only a small fraction of the total lung volume, and hence usually asymptomatic, is in patients treated for breast tumors. Therefore, the present, retrospective study was initiated in 451 patients to address the question of dependence of radiation pneumopathy on age and hormonal treatment at the time of radiotherapy. Moreover, the relationship between early pneumopathy (pneumonitis) and late radiation sequelae (fibrosis) was analyzed. All patients received homogeneous radiation exposure of the lung with 2.0 Gy per fraction to total doses of 50–60 Gy in strictly conventional, daily fractionated protocols, thus excluding effects of varying dose per fraction. Moreover, to avoid confounding effects of cytostatic drugs, patients receiving combined radiochemotherapy were excluded from the analysis.

The irradiated volumes varied significantly with patient group (ME vs. BCT), but also with the patient's anatomy. Based on two-dimensional treatment planning only, the present data do not allow for an analysis of the volume effect.

Clinical symptoms of pneumonitis in the present study were found in 5.5% of the patients at 6–8 weeks after the end of radiotherapy. All patients with clinical symptoms also had radiologic signs of pneumonitis at 15 weeks. The highest incidence of clinical pneumonitis was observed in the ME group and no reactions in the group with exclusive irradiation of the breast, despite higher doses in the BCT groups, particularly the group with inclusion of the axilla in the treatment volume (BCT1). It is well known from preclinical [11] and clinical studies [17, 30, 32] that – in contrast to radiologic changes – clinical symptoms of pneumopathy are highly dependent on the lung volume exposed, and hence this difference can be attributed to the smaller irradiated volume in the BCT groups. Corresponding data from the literature range between 0% and 34% [5, 16, 22, 25], with higher incidences associated with a higher number of fields, again indicating the volume effect for symptomatic radiation reactions. However, these data may be confounded by different definitions of the clinical endpoints as well as by variations in the intensity of the examinations.

Early radiologic changes in the present study were defined at 15 weeks after the end of radiotherapy. The incidence was 37% in the ME group, 18% in the BCT1 group, and 4% in group BCT2. According to Slanina et al. [30], maximum radiologic changes reflecting pneumonitis occur between 14–20 weeks after the onset of radiotherapy, and hence the endpoint in the present study reflects pneumonitis progressing into

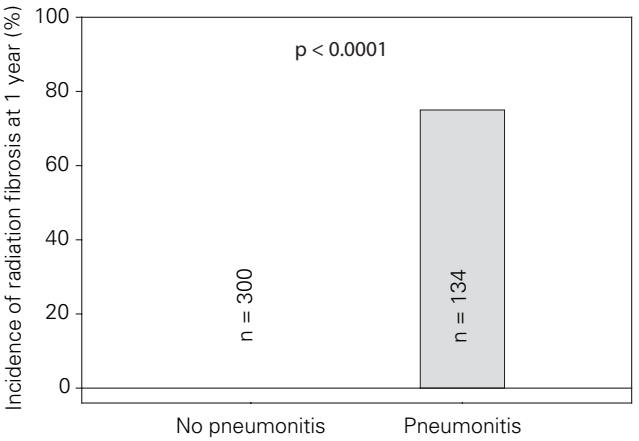

Figure 4. Frequency of radiographic changes in irradiated lung tissue at 1 year or later, reflecting fibrosis, in patients without or with positive radiographic changes (standard chest radiography) at 15 weeks after radiotherapy. Numbers of patients are given at the bars. The p-value is based on univariate analysis.

Abbildung 4. Häufigkeit radiologischer Veränderungen im bestrahlten Lungengewebe (Fibrose) nach 1 Jahr oder später bei Patientinnen ohne bzw. mit radiologischen Veränderungen in der Standard-Thoraxaufnahme nach 15 Wochen. Die Zahl der Patientinnen ist angegeben. Der p-Wert resultiert aus der univariaten Analyse.

early fibrosis, including early shrinkage processes. The latter, particularly close to the pleura, may have prevented detection of a fraction of pneumonitic/fibrotic changes, particularly in very small volumes, in the present study. As volumes in the BCT groups were significantly smaller than in the ME group, this may explain the lower incidence of radiologic changes in the BCT groups, which were observed despite higher doses compared to the ME group. The incidence for early radiologic changes in the literature varies between 0–63%, again depending on the method of detection (radiographs vs. CT) and the time of the examination relative to radiotherapy, as well as inclusion of radiochemotherapy patients.

In the present study, a highly significant influence of age on the incidence of early pneumopathy (pneumonitis) was observed. Similar observations were made by Slanina et al. [30]. In contrast, more recent studies in breast cancer patients [3, 9, 14, 22] and lung cancer patients [5, 18, 26] did not confirm the age dependence. While these more recent studies included correction for inhomogeneities in lung density for dose planning, this was not considered in the earlier studies, including the present investigation. Therefore, the age dependence may be attributed to the higher incidence of emphysema in older patients [9, 12]. However, further, prospective clinical data are required to clarify the effect of age on the development of (radiologic) radiation pneumonitis.

The administration of tamoxifen had a highly significant effect on the development of radiation pneumonitis in uni- and multivariate analyses. This has also been demonstrated (for lung fibrosis) by Bentzen et al. [3] in 196 breast cancer

patients. Similarly, Huang et al. [14] report a significant effect of tamoxifen in 109 patients. Jancke et al. [15] report an increase in pulmonary changes in CT scans by tamoxifen in a total of 422 breast cancer patients, which, however, did not reach statistical significance. Similarly, Wennberg et al. [33] did not observe an effect of tamoxifen on CT assessed lung changes in 121 patients.

Basis for the effect of tamoxifen may be an induction of transforming growth factor (TGF-)β [1, 3], which is a key molecule in the early signaling cascade eventually resulting in fibrosis [4, 7, 10, 13, 21, 23].

In the present study, the vast majority (75%) of early radiation-induced changes at 15 weeks progressed into *radiologic symptoms at 1 year*. In none of the patients without an early response, a fibrotic lesion was detected. This indicates a strong consequential component in late radiation pneumopathy. Similar observations have been made by Slanina et al. [30], Polansky et al. [20], and Steidle [31]. By contrast, Fröhlich [8] reported fibrosis without preceding pneumonitis in 12/105 patients despite a high frequency of examinations. Interestingly, the factors affecting early pneumopathy, i.e., treatment group, age and tamoxifen administration, all were without an independent effect on changes after 1 year, when early pneumopathy was included as a source parameter in the multivariate analysis. This indicates that, once initiated, the processes eventually becoming clinically manifest as late pneumopathy, are independent of the original cause.

Recent radiobiological studies, summarized in Dörr & Herrmann [7] demonstrated, that the development of radiation pneumopathy is a complex dynamic process, which is initiated immediately after the exposure to radiation, and which progresses over long time periods, although in some phases at a subclinical level without morphological or functional changes, i.e., during the "latent time" of the radiation effect. Therefore, a strong interaction between the individually identifiable response phases, clinically or by other diagnostic means, must be expected.

The influence of the diagnostic procedure on the results is demonstrated in the present study, when patients with radiographically negative responses at 1 year, which were positive at 15 weeks, were reexamined with CT or HR-CT. In 20/21 of these patients the more sensitive procedures revealed fibrotic changes, and only one patient remained without diagnosis of fibrosis. The higher sensitivity of three-dimensional reconstructive procedures was repeatedly reported [2, 5, 15, 25, 27].

The strong consequential component in the development of radiation pneumopathy indicates that early interventions in the pathogenetic process may be able to prevent late radiation fibrosis. The development of these approaches, however, requires interdisciplinary approaches [6, 19] including molecular, cell and radiobiologists, medical physicists, and radiation oncologists.

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