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Review Article

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Effect of Adjuvant Hormonal Therapy on the Development of Pulmonary Fibrosis after Postoperative Radiotherapy for Breast Cancer

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ABSTRACT

Breast cancer is the most common malignancy among women. Therefore, it is of paramount importance to study the adverse effects of oncological treatment of breast cancer, with one of adverse effects being pulmonary fibrosis (PF). PF is an irreversible condition and can significantly reduce the quality of life. Following lumpectomy, radiotherapy is the standard adjuvant treatment for breast cancer. Additionally, hormone receptor-positive breast cancers are treated with adjuvant hormonal therapy. While radiotherapy is one of the known causes of PF, the effect of hormone therapy on its development is not well-defined. Some studies have shown that the concomitant administration of endocrine therapy, primarily tamoxifen, and irradiation may potentiate the development of PF. However, guidelines regarding the timing of hormone therapy administration with respect to adjuvant radiotherapy are not clearly defined. This review aims to provide a comprehensive overview of the available information regarding the effect of hormone therapy and its timing of administration with respect to adjuvant radiotherapy on the incidence of PF.

Keywords: Breast neoplasms; Hormone antagonists; Pulmonary fibrosis; Radiotherapy; Tamoxifen

INTRODUCTION

Breast cancer (BC) is the leading type of cancer and the primary cause of cancer-related mortality in women [1,2]. Five-year relative breast cancer survival in the developed world is around 80% [3]. Treatment is multidisciplinary and may include surgery, radiotherapy (RT), chemotherapy, hormonal therapy (HT), and biologic therapy [4].

There are several subtypes of BC. To identify the BC subtype, tissue is routinely tested for the presence of estrogen receptor (ER) and progesterone receptor (PR) by immunohistochemical testing [1]. BC that has at least 1% of the tumor cells positive for ER or PR is classified as hormone receptor-positive BC and treated with adjuvant HT [4]. Estrogen and its metabolites play a key role in the proliferation of hormone receptor-positive BC [5]. Tamoxifen (TAM) can be used as an HT in postmenopausal and premenopausal patients [6]. It binds competitively to the ER and thus prevents estrogen-induced activation of signaling pathways [5]. In ER

positive patients, adjuvant treatment with TAM reduces the BC recurrence rate by 39% and annual BC death rate by 31% [6]. Treatment with TAM with or without ovarian suppression is advised in premenopausal patients [4].

For postmenopausal patients with hormone receptor-positive BC, an aromatase inhibitor (AI), which is another type of HT, is advised as an initial adjuvant HT [4]. Several types of AIs, such as letrozole, anastrozole, and exemestane, are used as an adjuvant therapy. No statistically significant differences in efficacy have been demonstrated among them [5,7]. They inhibit the activity of the enzyme aromatase that converts androgen precursors to estrogens. Aromatase is expressed in ovaries and also in extragonadal tissue such as the subcutaneous fat, brain, liver, bones, endothelium, and breast fat [8]. However, aromatase inhibitors are not effective in patients with viable ovaries [4]. Before menopause, ovarian aromatase is responsible for most of the circulating estrogen, whereas after menopause, aromatase in the fat and muscles is largely responsible for it [9].

Radiotherapy is the standard adjuvant treatment following lumpectomy in BC patients with both positive and negative lymph nodes. Overall, irradiation after lumpectomy has been shown to reduce the 10-year recurrence rate by 15.7% and the probability of death due to BC after 15 years by 3.8% [10].

While the guidelines for adjuvant HT according to patient age and associated diseases are clear, the optimal timing of HT with respect to adjuvant irradiation is not yet clearly defined. Additionally, the effect of HT on the incidence of pulmonary fibrosis (PF) is not well defined [11].

PULMONARY FIBROSIS

PF is an irreversible condition which is a component of over 200 interstitial lung diseases (ILDs). ILDs are a group of diseases that are characterized by chronic inflammation and progressive fibrosis of the pulmonary interstitium. ILDs can be broadly classified into the following categories: ILDs with a known etiology (environmental factors, drugs, hypersensitivity reactions, infections, irradiation), ILDs associated with systemic abnormalities (sarcoidosis, collagen vascular disorders), idiopathic interstitial pneumonias (IIPs), and some rare conditions such as eosinophilic granuloma [12].

The pathogenesis of PF is poorly understood. Genetic and environmental causes play a significant role [12]. A 3-phase model has been proposed; however, it cannot be applied to all pulmonary fibrotic conditions such as injury, inflammation, and repair. In most pulmonary fibrotic conditions, dysregulation of at least 1 of these 3 phases is common. Chronic inflammation can lead to an inadequate secretion of cytokines, chemokines, growth factors, and fibrogenic factors. This can result in an increased accumulation of the extracellular matrix, which results in the destruction of the normal pulmonary architecture. However, the cause of the most common group of PF, idiopathic pulmonary fibrosis (IPF), is unknown [13].

In majority of the patients, PF manifests as cough, shortness of breath, and dyspnea. Other clinical features depend on the etiology, which has important prognostic and treatment implications [14]. In addition to clinical examination, pulmonary function tests can be performed, which usually show a restrictive pattern of lung dysfunction with a reduced forced vital capacity (FVC), total lung capacity (TLC), and carbon monoxide diffusing capacity

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(DLCO). Non-contrast high-resolution computed tomography (HRCT) is the key imaging modality in the PF diagnostic procedure. Different radiologic patterns can be observed in different ILDs; they may be seen as reticular interstitial patterns and honeycomb lung changes with or without traction bronchiectasis and lung architectural distortion. If a final diagnosis of PF still cannot be made, bronchoalveolar lavage (BAL) or pulmonary biopsies are often performed to evaluate radiologically suspected PF [15]. There are 3 distinct patterns of PF that can be identified in histological specimens: usual interstitial pneumonia (UIP), fibrotic nonspecific interstitial pneumonia (fNSIP), and airway-centered fibrosis (ACF). The different histologies of these 3 types are primarily based on the distribution of fibrosis (diffuse or patchy) and on anatomical localization (subpleural, paraseptal, interstitial, airway-centered). These PF patterns are the basis for determining the underlying etiology [14].

The most common subtype of UIP is IPF. UIP (especially IPF) has the worst prognosis among all interstitial lung diseases [14]. IPF has a 5-year survival rate of only 20%, indicating a lack of effective therapies [16]. Similar to the ACF subtype, fNSIP has a better prognosis than UIP. ACF is reported to have a 5-year overall survival (OS) rate of 67.5% [14].

Treatment depends on the etiology. The identification and elimination of the antigen is of paramount importance. Steroids are not effective in the chronic phase of the disease. Treatment strategies for IPF have not been well defined until recently. It has been demonstrated that the treatment of IPF with standard therapy consisting of prednisolone, azathioprine, and N-acetyl cysteine increases the risk of death or hospitalization [17]. Recently, antifibrotic agents have been registered for use in the treatment of IPF but not for other subtypes of UIP [14].

Pulmonary fibrosis and radiotherapy

As previously mentioned, irradiation is one of the known causes of ILD. Irradiation-induced damage to the lung tissue occurs in 5%–15% of BC patients treated with adjuvant RT[18]. Although patients may have no clinical signs, clinically significant symptomatic lung injury occurs in 1%–5% of the patients [19]. The presenting symptoms are dyspnea, cough, and mild fever [20]. In the acute phase, the injury manifests as pneumonitis, which may occur up to 6 months after the end of RT, and is limited to the irradiated field [20,21]. Milder lung tissue lesions usually heal without treatment. However, more extensive lesions may progress to PF within 6–12 months after RT [21].

In the pathogenesis of radiation-induced lung tissue injury, numerous cytokines (interleukin [IL]-1, tumor necrosis factor alpha, platelet-derived growth factor, transforming growth factor [TGF]-β), cell types (macrophages, epithelial cells, pneumocytes, fibroblasts), and gene products are involved, similar to other ILDs [22-24]. The damage to the capillary endothelium and alveolar epithelium (type I cells [epithelial lining cells] and type II cells [surfactant-producing cells]) is of particular importance and leads to a decrease in the lung volume and diffusing lung capacity [21].

The treatment of choice is steroids, which are used primarily for pneumonitis and symptomatic therapy. Most experts agree that corticosteroids have no place in the treatment of radiation-induced PF [21].

An increased extent or severity of radiation-induced damage is associated with a larger irradiated volume, higher total delivered dose of radiation, and with hypofractionation [21]. Age is the

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most important predictive factor for the occurrence of radiation-induced pulmonary toxicity [25]. The effect of smoking during RT on the occurrence of pulmonary injury has not yet been clarified; the results of studies are conflicting [26]. Studies have also shown that the concomitant administration of HT, primarily TAM, with RT may be a risk factor for PF [20]. Since only a small proportion of patients experience symptomatic lung injury, it is difficult to detect the effect of different risk factors, including the addition of HT to RT, on the occurrence of lung damage.

EFFECT OF TAMOXIFEN IN CONJUNCTION WITH ADJUVANT RADIOTHERAPY ON THE OCCURRENCE OF PULMONARY FIBROSIS

There are few reports on the effect of TAM alone on the incidence of lung injury in patients who have not received irradiation. In the literature, we found 2 case reports describing lung injury after TAM administration. Etori et al. [27] reported the case of a 74-year-old patient with BC who received adjuvant TAM. Due to a cough, computed tomography (CT) was performed after 3 months, and ground-glass opacification was observed. Ahmed and Shahid [28] described the case of a 66-year-old lady with BC who also started adjuvant therapy with TAM and developed coughing within a week. She was diagnosed with acute interstitial pneumonitis. Despite limited data, both reports concluded that TAM alone can, although infrequently, cause lung damage.

A small number of prospective and retrospective studies have examined the association between the occurrence of PF and TAM treatment in conjunction with adjuvant RT (**Table 1**).

In a prospective randomized study from 1996, Bentzen et al. [29] examined the effect of TAM on the incidence of PF in patients treated with mastectomy and adjuvant RT with or without concomitant TAM. The occurrence of PF was monitored with chest X-ray regularly every 6 months and then yearly. They found a statistically significant 2-fold increase in PF if the patients had been receiving TAM.

Table 1. Effect of tamoxifen in conjunction with adjuvant radiotherapy on the incidence of pulmonary fibrosis

Reference	Year	Study design	Treatment groups	Number of subjects	Results
Bentzen et al. [29]	1996	Prospective, randomized	· RT + TAM · RT alone	· 38 patients · 46 patients	· 2-fold increase in PF if patients received TAM (S)
Koc et al. [30]	2002	Prospective	· RT + TAM · RT alone	· 74 patients · 46 patients	· Increase in PF (35% vs. 14%) if patients received TAM (S)
Varga et al. [31]	2011	Prospective	· CT → *RT · RT + TAM/AI · RT alone	· 79 patients · TAM 77 patients/AI 82 patients · 90 patients	· Increase in PF if patients received TAM (S)
Dörr et al. [32]	2005	Retrospective	· RT + TAM · RT alone	· 221 patients · 230 patients	· Increase in early pneumopathy if patients received TAM (S) · 75% of early pneumopathies progressed to PF after 1 year
Yavas et al. [33]	2013	Prospective	· Control group · RT alone · TAM alone · Anastrozole alone · Letrozole alone · RT + TAM · RT + anastrozole · RT + letrozole	· 80 rats	· Higher incidence of PF in group with concomitant TAM (S) · No significant difference in PF score in TAM alone group

RT = adjuvant radiotherapy; TAM = tamoxifen; PF = pulmonary fibrosis; S = statistically significant *p*-value; CT = chemotherapy; AI = aromatase inhibitor.
*Sequential.

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In 2002, Koc et al. [30] published a prospective study in which they investigated the development of PF following post-mastectomy RT with Cobalt-60. The patients either received TAM concomitantly or were only irradiated. They were monitored with CT at 3- to 4-month intervals in the first year, 4- to 6-month intervals in the second year, and then yearly. Univariate analysis demonstrated significantly more grades 2 and 3 PF after 48 months according to the Radiation Therapy Oncology Group (RTOG) Late Toxicity Criteria in those receiving TAM along with irradiation. Multivariate analysis showed that age and menopausal status were independent prognostic factors for the onset of PF in the TAM-receiving group of patients.

In a prospective study from 2001, Varga et al. [31] used more advanced RT techniques (3-dimensional [3D] conformal RT). Patients who underwent lumpectomy or mastectomy and adjuvant RT were enrolled. Some of them also received chemotherapy with taxanes before RT or concomitant HT with AI/TAM. The patients were monitored with CT 3 months and 1 year after the completion of RT, regardless of the clinical signs and symptoms. Grade 1 PF, according to the Common Toxicity Criteria version 2.0, was used to describe the new appearance of fibrotic abnormalities in the radiation fields. A total of 40.8% of the patients who received TAM were diagnosed with PF and multivariate analysis confirmed the significant effect of TAM on the incidence of PF. However, this was not the case for AI and taxane chemotherapy.

Dörr et al. [32], in their study published in 2005, evaluated the effect of age and TAM used concurrently with adjuvant RT after mastectomy or breast conservation surgery on the occurrence of pneumonitis and, consequently, PF. Lungs were imaged with a chest X-ray 15 weeks after the end of RT to assess pneumonitis and 1 year after RT to evaluate PF. Pneumonitis was radiologically defined as increased density, hazy opacity, and strand-like densities, while fibrosis was defined as dense strand-like residues, fibrotic strands, and mediastinal dislocations. The radiological assessment did not necessarily reflect the clinical consequences. Early radiologic changes were detected in 29.7% of patients, while clinical symptoms of pneumonitis were seen in 5.5% of patients. Age above 58 years and TAM therapy were found as significant parameters of early pneumopathy, which developed in 38.9% of the patients on TAM. Overall, 75% of early pneumopathies progressed to fibrosis after 1 year.

In 2012, Yavas et al. [33] published a study in which Whistar albino rats were randomized to 8 groups with different treatment plans that included only RT, HT, or RT with HT (**Table 1**). The lungs were irradiated with 12 Gy in one fraction. The extent of PF was quantified by an image analysis of the histological sections of the lung. A significantly higher incidence of PF was observed in patients who received concurrent TAM and radiation than in those who received only irradiation. TAM alone, without concomitant RT, had no effect on the incidence of PF.

As shown by previous studies, TAM in conjunction with RT may increase the incidence of PF. The key mechanism is via the induction of TGF-β synthesis. TGF-β is a cytokine that plays an important role in controlling tissue proliferation and differentiation in most human epithelial tissues. It plays a vital role in the development of tissue fibrosis including PF [34,35]. In mammals, it has 3 isoforms, TGF-β1, TGF-β2, and TGF-β3, which have almost identical biological characteristics. TGF-β binds to at least 3 membrane proteins, the most important being type I and II receptors, which are transmembrane serine-threonine kinases. TGF-β causes an increase in the synthesis and deposition of the extracellular matrix, a major pathological feature of fibrotic disease, via the type I receptor. Additionally, TGF-β1 is highly chemotactic for neutrophils, lymphocytes T, monocytes, and fibroblasts. It also regulates other growth factors that are important for the process of healing after damage and subsequent fibrosis.

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Another well-known effect of TGF-β is an increase in the cell adhesion to the matrix. Moreover, it enhances its own production in cells, further increasing the response [34].

Butta et al. [35] studied the effect of TAM on the regulation of TGFβ *in vivo*. Tru-cut biopsies obtained from 10 patients with BC before and after 3 months of treatment with TAM were analyzed. Only a very weak signal that indicated the presence of TGF-β1 in and around stromal fibroblasts and epithelial cells was detected in biopsy specimens taken prior to TAM treatment. Three months after TAM therapy, a dramatic increase in the extracellular TGF-β1 was detected in repeated biopsies in all 10 patients. TGF-β1 was located primarily between and around the stromal fibroblasts, suggesting the possibility that TAM induced the synthesis of TGF-β1 in these cells.

Colletta et al. [36] used 2 human fetal fibroblast strains (from the lung and pituitary gland) as models for BC stromal fibroblasts. The addition of subtoxic amounts of TAM to both fibroblast strains resulted in a significant induction of TGF-β synthesis. The fibroblast strains from the pituitary gland responded with a 27-fold increase in TGF-β induction, while those from the lungs exhibited a 5-fold increase.

EFFECT OF AROMATASE INHIBITORS IN CONJUNCTION WITH ADJUVANT RADIOTHERAPY ON THE OCCURRENCE OF PULMONARY FIBROSIS

The widespread use of third generation AIs began in the 1990s, almost 2 decades after the use of TAM [37]. Therefore, there is less information regarding the effect of AI on the incidence of PF.

In 2016, Altinok et al. [38] published a study in which 60 Whistar albino rats were divided into 6 groups with different treatment plans consisting of RT alone or RT with concomitant TAM/anastrozole/letrozole/exemestane. The irradiation dose to the thoracic region comprised 30 Gy in 10 fractions. PF was identified by an image analysis of the histological sections of the lung. Significantly less PF was observed in the groups treated with concomitant AI than in the TAM-treated or irradiated-only groups. Additionally, there were no significant differences between the various AIs. A protective mechanism of AIs against the development of PF has been suggested but has not been elucidated yet.

EFFECT OF THE ADJUVANT RADIOTHERAPY AND HORMONAL THERAPY SEQUENCE ON LUNG TOXICITY

Sequential or concomitant use of tamoxifen with adjuvant radiotherapy

In studies examining the effect of TAM on the incidence of PF, TAM was mostly used concomitantly with RT; however, some studies have revealed that there may be a difference in the incidence of PF depending on whether the 2 treatments are given in a concomitant or sequential manner.

Animal models have suggested that there may be a greater risk of PF development with concomitant TAM administration. Bese et al. [39] in 2004 published a study in which Wistar albino rats were irradiated and randomized into 3 groups with different treatment

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Table 2. Effect of concomitant or sequential use of tamoxifen with adjuvant radiotherapy on the incidence of pulmonary fibrosis

Reference	Year	Study design	Treatment Groups	Number of subjects	Results
Bese et al. [39]	2006	Prospective	· RT → *TAM · RT + TAM · RT alone	· 24 rats	· Higher incidence of PF if TAM administered concomitantly (S)
Pierce et al. [40]	2005	Retrospective analysis	· RT → TAM · RT + TAM	· 107 patients · 202 patients	· Only 1 Grade 3 pulmonary toxicity in the group with concomitant TAM; none in the group with sequential TAM (NS)
Harris et al. [41]	2005	Retrospective	· RT → TAM · RT + TAM	· 104 patients · 174 patients	· Only 1% of pts had pneumonitis in the group with concomitant TAM; none in the group with sequential TAM (NS)
Munshi et al. [42]	2011	Prospective, randomized	· RT → TAM · RT + TAM	· 260 patients	· No results published yet

RT = adjuvant radiotherapy; TAM = tamoxifen; PF = pulmonary fibrosis; S = statistically significant *p*-value; NS = not significant *p*-value.
*Sequential.

plans that included either sequential or concomitant administration of TAM. The rats were administered a radiation dose of 30 Gy in 10 fractions to the thoracic region. PF was identified by an image analysis of the histological sections of the lung. Compared to the other 2 groups, TAM administered concomitantly with RT resulted in a higher incidence of PF, which was observed in 37% of the rats in that group (**Table 2**).

However, 2 retrospective studies [40,41] published in 2005 did not confirm the results of the study above. Neither of them demonstrated any differences in lung toxicity (**Table 2**). Pierce et al. [40] retrospectively analyzed groups of BC patients from the Southwest Oncology Group trial 8897 (Intergroup 0102), who were treated with chemotherapy, RT, and TAM (in a sequential or concomitant manner). No significant differences in lung toxicity were observed between the groups. In addition, the timing of TAM administration did not affect the outcome of the treatment. After 10.3 years of median follow-up, there were no statistically significant differences in the OS, disease-free survival (DFS), and local recurrence rate (LRR). Similarly, a retrospective study by Harris et al. [41] also did not identify differences between the concomitant or sequential use of TAM. While pneumonitis was reported in only 1% of the patients in the group that received concomitant TAM, it was not seen in the group that received sequential treatment. Moreover, there were no statistically significant differences in the 10-year LRR, OS, and recurrence-free survival (RFS) between the 2 groups. Chemotherapy did not affect the results.

In the literature, there is also information about a trial named "Concurrent Versus Sequential Tamoxifen with Radiotherapy in Breast Cancer Patients (CONSET)" [42], but the results have not been published yet. In this trial, 260 BC patients who had undergone conservative surgery or mastectomy were randomized to receive either TAM concomitantly or sequentially with RT. The primary aim of this study is to evaluate the incidence of PF, while the secondary aim is to examine the rate of locoregional and distal recurrences. The study results may thus provide a clearer answer to the question whether the timing of TAM administration affects the onset of PF.

Sequential or concomitant use of aromatase inhibitors with adjuvant radiotherapy

In the previously mentioned studies by Yavas et al. [33] and Altinok et al. [38] on Whistar albino rats, no increase in the incidence of PF was observed after RT with concomitant administration of AI. There are 2 additional studies in the literature on this subject with a similar result (**Table 3**).

The prospective randomized study CO-HO-RT [43], included postmenopausal BC patients treated with adjuvant RT and letrozole in a concurrent or sequential manner. Pulmonary toxicity was

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Table 3. Effect of concomitant or sequential use of aromatase inhibitors with adjuvant radiotherapy on the incidence of pulmonary fibrosis

Reference	Year	Study design	Treatment Groups	Number of subjects	Results
Azria et al. [43]	2010	Prospective, randomized	· RT → *letrozole · RT + letrozole	· 75 patients · 75 patients	· No lung toxicity detected
Ishitobi et al. [44]	2009	Retrospective	· RT → AI · RT + AI	· 151 patients · 113 patients	· Only 1 Grade 3 pneumonitis in the group with concomitant AI; none in the group with sequential AI (NS)

RT = adjuvant radiotherapy; AI = aromatase inhibitor; NS = not significant *p*-value.
*Sequential.

monitored by performing clinical examinations, pulmonary function tests, and CT at 6-month intervals for 2 years, and then on a yearly basis. No lung toxicity was detected after 2 years.

Ishitobi et al. [44] published a retrospective analysis in 2009, which similarly included postmenopausal BC patients following lumpectomy, who subsequently received adjuvant RT and AI, either concomitantly or sequentially. According to the RTOG Late Toxicity Criteria, only one patient developed G3 pneumonitis in the concomitant AI group (1%) and none in the sequential group. There was no difference between the 2 groups with respect to the 3-year ipsilateral recurrence, OS, and RFS rates.

Meta-analysis

In 2016, a meta-analysis [45] of studies examining the concomitant or sequential use of HT with RT in patients after BC surgery was conducted in China. The primary goal of the study was to evaluate the appearance of pneumonitis or PF. A total of 11 studies were included, 10 of which were retrospective and 1 prospective. Four studies examined the use of TAM, 4 AI, and 3 studies allowed the patients to receive either TAM or AI. A total of 1,291 patients received HT concomitantly with RT whereas 1,179 patients received them sequentially. Two studies reported cases of greater than grade 2 radiation pneumonitis and 5 studies reported cases of PF. There were no statistically significant differences in the incidence of pneumonitis or PF. Furthermore, no statistically significant differences were observed in the 5- and 10-year OS, LR, and occurrence of distant metastases.

CONCLUSION

Pulmonary fibrosis is an irreversible form of lung injury, that may rarely develop as an adverse effect of oncological treatment in BC patients. Some forms of PF have a poor prognosis, with a 5-year survival rate of only about 20%.

Preclinical studies have revealed that TAM induces the synthesis of TGF-β, which plays a key role in the development of tissue fibrosis. Clinical studies comparing RT with or without TAM therapy have generally found higher rates of PF in patients who received TAM in addition to RT. In contrast, AIs do not increase the incidence of PF.

Furthermore, only animal models have shown that the concomitant administration of TAM with RT may result in an increased incidence of PF. However, clinical retrospective studies, including the meta-analysis, did not demonstrate significant differences in pulmonary toxicity with regard to the timing of TAM administration.

The above listed studies have many limitations. In addition to majority of them being old and retrospective studies, some of them used older radiation techniques or included a

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small number of patients. They utilized different diagnostic approaches for the evaluation of lung toxicity and different time intervals. In majority of the studies, the diagnosis of PF was based on imaging, which in some studies was limited to only a chest X-ray with no pulmonary function tests being performed. Some of the studies also did not report the types of diagnostic procedures that were used. There is also a lack of data from larger modern prospective randomized studies, therefore the results of the prospective randomized study CONSET are highly awaited.

Importantly, the incidence of clinically evident PF after RT is very low. Consequently, it is very difficult to detect a difference after adding HT to RT in routine clinical practice. In the future, to increase sensitivity, patients with subclinical ILD might be identified with the help of validated patient-reported outcome measures, specifically designed for BC patients treated with adjuvant RT and HT. This could be the next step in studying the effect of combined RT and HT on lung toxicity.

As there are millions of BC patients in the world who have been treated with adjuvant RT and HT, a clarification regarding the effect of oncological treatment on lung tissue is of paramount importance.

REFERENCES

1. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res 2017;50:33.
PUBMED | CROSSREF
2. Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJ, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet 2011;378:1461-84.
PUBMED | CROSSREF
3. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol 2008;9:730-56.
PUBMED | CROSSREF
4. Breast Cancer – v.3. 2019. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed December 15th, 2019.
5. Schneider R, Barakat A, Pippen J, Osborne C. Aromatase inhibitors in the treatment of breast cancer in post-menopausal female patients: an update. Breast Cancer (Dove Med Press) 2011;3:113-25.
PUBMED | CROSSREF
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
PUBMED | CROSSREF
7. Lønning PE. The potency and clinical efficacy of aromatase inhibitors across the breast cancer continuum. Ann Oncol 2011;22:503-14.
PUBMED | CROSSREF
8. Nelson LR, Bulun SE. Estrogen production and action. J Am Acad Dermatol 2001;45:S116-24.
PUBMED | CROSSREF
9. Fabian CJ. The what, why and how of aromatase inhibitors: hormonal agents for treatment and prevention of breast cancer. Int J Clin Pract 2007;61:2051-63.
PUBMED | CROSSREF
10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-16.
PUBMED | CROSSREF

11. McGee SF, Mazzarello S, Caudrelier JM, Lima MA, Hutton B, Sienkiewicz M, et al. Optimal sequence of adjuvant endocrine and radiation therapy in early-stage breast cancer - A systematic review. Cancer Treat Rev 2018;69:132-42.
PUBMED | CROSSREF
12. Green FH. Overview of pulmonary fibrosis. Chest 2002;122:334S-339S.
PUBMED | CROSSREF
13. Wilson MS, Wynn TA. Pulmonary fibrosis: pathogenesis, etiology and regulation. Mucosal Immunol 2009;2:103-21.
PUBMED | CROSSREF
14. Smith ML. Update on pulmonary fibrosis: not all fibrosis is created equally. Arch Pathol Lab Med 2016;140:221-9.
PUBMED | CROSSREF
15. Meyer KC. Pulmonary fibrosis, part I: epidemiology, pathogenesis, and diagnosis. Expert Rev Respir Med 2017;11:343-59.
PUBMED | CROSSREF
16. Wuyts WA, Agostini C, Antoniou KM, Bouros D, Chambers RC, Cottin V, et al. The pathogenesis of pulmonary fibrosis: a moving target. Eur Respir J 2013;41:1207-18.
PUBMED | CROSSREF
17. Idiopathic Pulmonary Fibrosis Clinical Research NetworkRaghu G, Anstrom KJ, King TE JrLasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968-77.
PUBMED | CROSSREF
18. Marks LB, Yu X, Vujaskovic Z, Small W Jr, Folz R, Anscher MS. Radiation-induced lung injury. Semin Radiat Oncol 2003;13:333-45.
PUBMED | CROSSREF
19. Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76:S70-6.
PUBMED | CROSSREF
20. Meattini I, Guenzi M, Fozza A, Vidali C, Rovea P, Meacci F, et al. Overview on cardiac, pulmonary and cutaneous toxicity in patients treated with adjuvant radiotherapy for breast cancer. Breast Cancer 2017;24:52-62.
PUBMED | CROSSREF
21. Abid SH, Malhotra V, Perry MC. Radiation-induced and chemotherapy-induced pulmonary injury. Curr Opin Oncol 2001;13:242-8.
PUBMED | CROSSREF
22. Rubin P, Finkelstein J, Shapiro D. Molecular biology mechanisms in the radiation induction of pulmonary injury syndromes: interrelationship between the alveolar macrophage and the septal fibroblast. Int J Radiat Oncol Biol Phys 1992;24:93-101.
PUBMED | CROSSREF
23. Rubin P, Johnston CJ, Williams JP, McDonald S, Finkelstein JN. A perpetual cascade of cytokines postirradiation leads to pulmonary fibrosis. Int J Radiat Oncol Biol Phys 1995;33:99-109.
PUBMED | CROSSREF
24. Vujaskovic Z, Marks LB, Anscher MS. The physical parameters and molecular events associated with radiation-induced lung toxicity. Semin Radiat Oncol 2000;10:296-307.
PUBMED | CROSSREF
25. Gagliardi G, Bjöhle J, Lax I, Ottolenghi A, Eriksson F, Liedberg A, et al. Radiation pneumonitis after breast cancer irradiation: analysis of the complication probability using the relative seriality model. Int J Radiat Oncol Biol Phys 2000;46:373-81.
PUBMED | CROSSREF
26. Kahán Z, Csenki M, Varga Z, Szil E, Cserháti A, Balogh A, et al. The risk of early and late lung sequelae after conformal radiotherapy in breast cancer patients. Int J Radiat Oncol Biol Phys 2007;68:673-81.
PUBMED | CROSSREF
27. Etori S, Nakano R, Kamada H, Hosokawa K, Takeda S, Fukuhara M, et al. Tamoxifen-induced lung injury. Intern Med 2017;56:2903-6.
PUBMED | CROSSREF
28. Ahmed S, Shahid RK. Acute interstitial pneumonitis following adjuvant tamoxifen therapy. J Clin Oncol 2009;27:e11637.
CROSSREF

29. Bentzen SM, Skoczylas JZ, Overgaard M, Overgaard J. Radiotherapy-related lung fibrosis enhanced by tamoxifen. J Natl Cancer Inst 1996;88:918-22.
PUBMED | CROSSREF

30. Koc M, Polat P, Suma S. Effects of tamoxifen on pulmonary fibrosis after cobalt-60 radiotherapy in breast cancer patients. Radiother Oncol 2002;64:171-5.
PUBMED | CROSSREF

31. Varga Z, Cserháti A, Kelemen G, Boda K, Thurzó L, Kahán Z. Role of systemic therapy in the development of lung sequelae after conformal radiotherapy in breast cancer patients. Int J Radiat Oncol Biol Phys 2011;80:1109-16.
PUBMED | CROSSREF

32. Dörr W, Bertmann S, Herrmann T. Radiation induced lung reactions in breast cancer therapy. Modulating factors and consequential effects. Strahlenther Onkol 2005;181:567-73.
PUBMED | CROSSREF

33. Yavas G, Yavas C, Acar H, Toy H, Yuce D, Ata O. Comparison of the effects of aromatase inhibitors and tamoxifen on radiation-induced lung toxicity: results of an experimental study. Support Care Cancer 2013;21:811-7.
PUBMED | CROSSREF

34. Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. N Engl J Med 1994;331:1286-92.
PUBMED | CROSSREF

35. Butta A, MacLennan K, Flanders KC, Sacks NP, Smith I, McKinna A, et al. Induction of transforming growth factor beta 1 in human breast cancer in vivo following tamoxifen treatment. Cancer Res 1992;52:4261-4.
PUBMED

36. Colletta AA, Wakefield LM, Howell FV, van Roozendaal KE, Danielpour D, Ebbs SR, et al. Anti-oestrogens induce the secretion of active transforming growth factor beta from human fetal fibroblasts. Br J Cancer 1990;62:405-9.
PUBMED | CROSSREF

37. Chumsri S, Howes T, Bao T, Sabnis G, Brodie A. Aromatase, aromatase inhibitors, and breast cancer. J Steroid Biochem Mol Biol 2011;125:13-22.
PUBMED | CROSSREF

38. Altinok AY, Yildirim S, Altug T, Sut N, Ober A, Ozsahin EM, et al. Aromatase inhibitors decrease radiation-induced lung fibrosis: results of an experimental study. Breast 2016;28:174-7.
PUBMED | CROSSREF

39. Bese NS, Umay C, Yildirim S, Ilvan S, Dirican A, Salar S, et al. The effects of tamoxifen on radiation-induced pulmonary fibrosis in Wistar albino rats: results of an experimental study. Breast 2006;15:456-60.
PUBMED | CROSSREF

40. Pierce LJ, Hutchins LF, Green SR, Lew DL, Gralow JR, Livingston RB, et al. Sequencing of tamoxifen and radiotherapy after breast-conserving surgery in early-stage breast cancer. J Clin Oncol 2005;23:24-9.
PUBMED | CROSSREF

41. Harris EE, Christensen VJ, Hwang WT, Fox K, Solin LJ. Impact of concurrent versus sequential tamoxifen with radiation therapy in early-stage breast cancer patients undergoing breast conservation treatment. J Clin Oncol 2005;23:11-6.
PUBMED | CROSSREF

42. Munshi A, Gupta D. Concurrent versus sequential radiotherapy and tamoxifen in breast cancer - The CONSET trial is launched. Acta Oncol 2011;50:154-5.
PUBMED | CROSSREF

43. Azria D, Belkacemi Y, Romieu G, Gourgou S, Gutowski M, Zaman K, et al. Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial. Lancet Oncol 2010;11:258-65.
PUBMED | CROSSREF

44. Ishitobi M, Komoike Y, Motomura K, Koyama H, Nishiyama K, Inaji H. Retrospective analysis of concurrent vs. sequential administration of radiotherapy and hormone therapy using aromatase inhibitor for hormone receptor-positive postmenopausal breast cancer. Anticancer Res 2009;29:4791-4.
PUBMED

45. Li YF, Chang L, Li WH, Xiao MY, Wang Y, He WJ, et al. Radiotherapy concurrent versus sequential with endocrine therapy in breast cancer: a meta-analysis. Breast 2016;27:93-8.
PUBMED | CROSSREF