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Prevalence and Characteristics of Pneumonitis Following Irradiation of Breast Cancer

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Abstract. *Background/Aim: Pneumonitis is a serious complication after radiotherapy of breast cancer. This study aimed to identify its prevalence and potential risk factors. Patients and Methods: A total of 606 patients irradiated following breast-conserving surgery or mastectomy were retrospectively analyzed. In patients developing pneumonitis, radiation and clinical parameters were investigated to identify potential risk factors. Results: Eleven patients (1.8%) developed a pneumonitis grade ≥2. Mean doses to the ipsilateral lung were >7 Gy in 5 patients (45%). Of the other patients, 5 had a chronic inflammatory disease. Six patients (55%) had another malignancy (4 previous contralateral breast cancers, 1 previous ovarian and thyroid cancer, 1 synchronous carcinoma-in-situ (pTis) at the contralateral breast). Five patients (45%) received chemotherapy including taxanes and 4 patients (36%) received trastuzumab. Conclusion: The prevalence of pneumonitis was 1.8%. Potential risk factors included mean radiation dose to ipsilateral lung >7 Gy, systemic treatment with taxanes or trastuzumab, chronic inflammatory disease and history of another malignancy.*

Breast cancer is the most common type of cancer in women in Europe and Northern America (1). Most patients with early-stage (T1- or T2-disease) tumors without lymph-node involvement receive breast conserving surgery followed by whole-breast irradiation (2). Patients with locally advanced cancer (T3- or T4-disease) generally receive mastectomy followed by radiotherapy of the chest wall. In case of involvement of axillary lymph nodes and presence of risk factors, regional lymph nodes may be included in the treatment volume after both breast-conserving surgery and mastectomy.

Radiotherapy of breast cancer is generally well tolerated with only minor toxicity such as erythema of the irradiated skin and fatigue. However, pneumonitis that may occur after several weeks following radiotherapy is a more serious side-effect (3). In a systematic review including data from 1995 to 2014, the prevalence of pneumonitis after radiotherapy of breast cancer patients ranged between 0.8% and 2.9% (4). However, in a more recent retrospective study of 515 patients, the pneumonitis rate was 3.7%, and in a prospective study, the rate of pneumonitis was 13% in patients who had received previous systemic treatment (3, 5). In order to define the current prevalence of pneumonitis after radiotherapy of breast cancer more precisely, additional studies of more recently treated patients are required. Therefore, we performed the present study in breast cancer patients irradiated between 2016 and 2019.

Patients and Methods

A total number of 606 female breast cancer patients who received radiotherapy following breast conserving surgery or mastectomy between January 2016 and May 2019 were retrospectively evaluated for radiation pneumonitis grade ≥2. This evaluation included patients who received postoperative irradiation to the whole-breast or the chest wall (plus/minus a boost to the tumor bed) with or without irradiation to supraclavicular plus/minus internal mammary lymph nodes. In patients who experienced pneumonitis, radiation and other clinical parameters were investigated to identify potential risk factors for the development of radiation pneumonitis. Radiation parameters included the treatment volume (whole-breast or chest wall plus/minus supraclavicular/internal mammary lymph nodes), administration of a radiation boost, prescribed radiation doses and dose-fractionation regimens, mean radiation doses to the ipsilateral lung, and use of the deep-inspiration breath hold (DIBH) technique. Clinical parameters included age at radiotherapy, tumor stage, histologic grading, estrogen and progesterone receptor status, HER-2 (human epidermal growth factor 2)/neu receptor status, relevant comorbidity and type of systemic treatment.

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Table I. *Radiation parameters of the 11 patients who developed pneumonitis.*

Patient number	Treatment volume	Radiation dose	Boost to tumor bed	DIBH technique	Mean dose to ipsilateral lung
1	Whole breast (right side)	50.4Gy (28×1.8Gy)	5×2.0Gy (sequential)	Yes	6.4Gy
2	Whole breast (left side)	50.4Gy (28×1.8Gy)	28×0.3Gy (SIB)	Yes	9.8Gy
3	Whole breast (left side)	50.4Gy (28×1.8Gy)	5×2.0Gy (sequential)	Yes	8.3Gy
4	Whole breast (left side)	50.4Gy (28×1.8Gy)	No	Yes	7.7Gy
5	Whole breast (right side)	50.4Gy (28×1.8Gy)	5×2.0Gy (sequential)	No	11.2Gy
6	Whole breast (left side)	40.0Gy (15×2.667)	5×2.0Gy (sequential)	Yes	4.3Gy
7	Right chest wall + lymph nodes*	50.4Gy (28×1.8Gy)	No	No	15.5Gy
8	Whole breast (bilateral)	40.0Gy (15×2.667)	No	No	6.9Gy (right side) 6.0Gy (left side)
9	Whole breast (right side)	29.3Gy** (11×2.667)	No	Yes	4.0Gy
10	Whole breast (right side)	40.0Gy (15×2.667)	5×2.0Gy (sequential)	No	6.8Gy
11	Whole breast (right side)	40.0Gy (15×2.667)	No	Yes	4.1Gy

DIBH: Deep inspiration breath hold; SIB: simultaneous integrated boost. *Supraclavicular and internal mammary lymph nodes; **Radiotherapy stopped due to pneumonitis (planned dose: 40 Gy without boost).

Results

Eleven patients (1.8%) were identified in the entire cohort of 606 patients who developed a pneumonitis grade ≥2 during or after radiotherapy of breast cancer. Pneumonitis was diagnosed after a median of 7.5 weeks (range=0–19 weeks) following radiotherapy.

All patients presented with progressive cough; 8 patients complained about dyspnea, and 3 patients had fever. All patients received prednisolone for up to 13 weeks, and pneumonitis resolved without sequelae in 9 patients. One patient required a second course of prednisolone (12 weeks), before resolution of pneumonitis resolved, and one patient still complained about dry cough and exertional dyspnea at 22 months following radiotherapy.

Of the 11 patients, 10 received whole-breast radiotherapy alone (plus a boost to the tumor bed in 6 patients) following breast conserving surgery (9 unilateral, 1 bilateral), and one patient received irradiation of the chest wall plus supraclavicular and internal mammary lymph nodes without a boost. The DIBH technique was used in 7 patients.

According to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), a mean lung dose of 7 Gy is associated with a 5%-risk of symptomatic (*i.e.* grade ≥2) radiation pneumonitis (6). In the present study, the mean dose to the ipsilateral lung was >7 Gy in 5 patients (7.7, 8.3, 9.8, 11.2 and 15.5 Gy). Of the other 6 patients, 5 patients had a chronic inflammatory disease (bronchial asthma n=2, rheumatoid arthritis n=2, rheumatoid arthritis plus Crohn's disease n=1).

Four of the 11 patients (36%) had previous contralateral breast cancer, one patient (9%) previous ovarian and thyroid cancer, and one patient (9%) synchronous carcinoma-in-situ (pTis) of the contralateral breast. The median age of the 11 patients developing pneumonitis was 59 years (range=43–80 years). None of the patients had a smoking history. All patients received systemic treatment prior or during radiotherapy. Five patients (45%) received chemotherapy including taxanes. Four patients (36%) received trastuzumab in addition to chemotherapy, which was combined with pertuzumab in 2 patients (18%).

Additional radiation parameters are summarized in Table I. Administered systemic treatments, tumor stages and histologic parameters are given in Table II.

Discussion

Many breast cancer patients receive radiotherapy. Since breast cancer is one of the most common cancers worldwide, a lot of research is performed in order to improve the outcomes after radiotherapy for the primary tumor and metastatic disease (7-13). Pneumonitis can be a serious complication of radiotherapy of malignancies within or adjacent to the thorax such as breast cancer, lung cancer and esophageal cancer.

Severe radiation pneumonitis has been reported to have a negative impact on the survival of patients irradiated for lung cancer (14). Pneumonitis after radiotherapy of breast cancer is less common than after radiotherapy of lung cancer. In most studies, pneumonitis rates in irradiated breast cancer patients were less than 3% (4). However, in a retrospective study of 515 irradiated breast cancer patients published in 2017, 3.7% (n=19) of the patients developed grade 2 radiation pneumonitis (5). In that study, the risk of pneumonitis was associated with the radiation dose to the ipsilateral lung. This agrees well with the findings of our present study, where the mean dose to the ipsilateral lung was >7 Gy in 5 of the patients (45%), which is generally considered to be associated with a pneumonitis risk of 5% (6). In 2004, a prospective study of 524 breast cancer patients compared chemotherapy with four cycles of paclitaxel followed by four cycles of 5-

Table II. *Systemic treatments, tumor stages and histologic parameters of the 11 patients who developed pneumonitis.*

Patient number	Chemotherapy	Other systemic treatment	Tumor stage	Histology, Grading	ER/PR status	*HER-2/neu* receptor status	*Ki-67* labeling index
1	6×Doc/Carbo (neoadjuvant)	TRA/PER Letrozol	cT2 cNx ypT0 ypN0	NST, G3	12/12	Positive	70%
2	4×EC/12×Pac (neoadjuvant)	TRA/PER Tamoxifen	cT1 cN+ ypT0 ypN0	NST, G3	12/8	Positive	15%
3	12×Pac (adjuvant)	TRA Tamoxifen	pT1b pN0	Lobular, G2	3/2	Positive	5%
4	No	Letrozol	pT1b pN0	NST, G1	+/+	Negative	5%
5	No	Letrozol	pT1c pN0	NST, G2	12/0	Negative	10%
6	No	Tamoxifen	pT1b pN0	NST, G1	9/12	Negative	5%
7	4×EC/12×Pac (adjuvant)	Tamoxifen	pT3 pN1a	NST, G3	12/1	Negative	17%
8	No	Tamoxifen	pT1 pN0 (R) pTis (L)	NST, G2 G3	12/6	Negative	6%
9	12×Pac (adjuvant)	TRA* Letrozol	pT1b pN0	NST, G3	12/0	Positive	15%
10	No	Tamoxifen	pT1a pN0	NST, G3	12/2	Negative	12%
11	No	Tamoxifen	pT1b pN0	NST, G1	12/6	Negative	5%

ER: Estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor 2; Doc: docetaxel; Carbo: carboplatin; TRA: trastuzumab; PER: pertuzumab; NST: no special type; EC: epirubicin/cyclophopsphamide; Pac: paclitaxel; (R): right side; (L): left side. *Trastuzumab stopped due to pneumonitis.

fluorouracil (5-FU), doxorubicin and cyclophosphamide (FAC) to 8 cycles of FAC (15). In that study, data of 189 patients (100 and 89 patients, respectively) receiving subsequent radiotherapy were available. Of these patients, 5% in the paclitaxel-FAC group and 4.5% in the FAC group, respectively, developed a clinically relevant pneumonitis. Moreover, taxanes have the potential to increase the risk of radiation pneumonitis and even to introduce pneumonitis independently of radiotherapy (3, 15-17). In the present study, 5 patients (45%) had received chemotherapy including taxanes. Trastuzumab, which was received by 4 patients (36%) in the present study, has also been reported to have the potential to lead to interstitial pneumonitis (18).

In addition to factors that are known to increase the risk of radiation pneumonitis, chronic inflammatory disease, namely bronchial asthma or rheumatoid arthritis, was present in 45% of our patients and, therefore, may be a risk factor for developing pneumonitis. Bronchial asthma is a chronic inflammatory disease of the lung, and rheumatoid arthritis may also affect the lungs (19, 20). Moreover, 55% of the patients in our study who developed pneumonitis had a history of another malignancy. One may speculate that these patients had a reduced DNA repair capacity, which has been described for several tumor entities (21-23). In addition, a study from Italy that compared 43 breast cancer patients to 34 healthy controls has suggested that breast cancer was associated with an impairment of the DNA repair capacity resulting in an increased radio-sensitivity and radiation toxicity (24). The results of these studies support the idea that patients with a history of an additional malignancy have reduced DNA repair capacity and a higher risk of developing radiation pneumonitis.

In summary, the prevalence of pneumonitis in this cohort of irradiated breast cancer patients was 1.8%. Potential risk factors for development of pneumonitis included a mean radiation dose to the ipsilateral lung of >7 Gy, systemic treatment with taxanes or trastuzumab, chronic inflammatory disease and history of another malignancy.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest related to this study.

Authors' Contributions

E.M.W., M.C.E., S.B. and D.R. participated in the design of the study. E.M.W., M.C.E., S.B. and D.R. provided data. E.M.W., M.C.E., S.B. and D.R. performed the analyses and the interpretation of the data. D.R. drafted the manuscript, which was reviewed and approved in its final form by all Authors.

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