Clinically Relevant Pneumonitis After Sequential Paclitaxel-Based Chemotherapy and Radiotherapy in Breast Cancer Patients

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Background: **Taxane-based chemotherapy has been associated with an increased risk of radiation pneumonitis in patients with breast cancer. To obtain additional information about this association, we investigated the association between paclitaxel chemotherapy and radiation pneumonitis in patients participating in a phase III randomized study.** ***Methods:*** **Five hundred and twenty-four breast cancer patients were prospectively and randomly assigned to receive either four cycles of paclitaxel followed by four cycles of 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) or eight cycles of FAC. One hundred and eighty-nine of these patients (100 in the paclitaxel–FAC group and 89 in the FAC group) subsequently underwent radiation therapy in our institution and had medical records available to review for pulmonary symptoms. In addition, a radiologist who was unaware of the type of treatment scored chest x-ray changes after radiation treatment. Crude rates of radiation pneumonitis were compared with chi-square or Fisher's exact test, and actuarial rates were assessed with Kaplan–Meier and log-rank tests. All statistical tests were two-sided.** ***Results:*** **No difference in the rate of clinically relevant radiation pneumonitis was observed between the two groups (5.0% in the paclitaxel–FAC group versus 4.5% in the FAC group; difference = 0.5%, 95% CI = −6.6% to 5.5%; $P = 1.00$). Oral steroids for pneumonitis were taken by two patients in the paclitaxel–FAC group but by none in the FAC group, and no patient was hospitalized for or died of radiation pneumonitis. The paclitaxel–FAC group (39.3%) had a higher rate of radiographic changes after irradiation than the FAC group (23.7%; difference = 15.6%, 95% CI = −0.11% to 28.8%; $P = .034$).** ***Conclusion:*** **Patients with breast cancer treated with sequential paclitaxel, FAC, and radiation therapy appeared to have a very low rate of clinically relevant radiation pneumonitis that was no different from that of patients treated with FAC alone. [J Natl Cancer Inst 2004;96: 1676–81]**

The use of taxanes has improved outcomes in patients with metastatic breast cancer *(1,2),* and randomized trials have found that addition of adjuvant therapy with taxane to an anthracycline-based chemotherapy regimen, compared with anthracycline-based chemotherapy alone, led to improved survival for patients with positive lymph nodes *(3,4).* Irradiation is also an important adjuvant therapy for breast cancer. Specifically, adjuvant radiation therapy for selected patients with breast cancer reduces locoregional recurrence and improves overall survival *(5–7).* However, this improvement in overall survival was achieved only after radiation therapy techniques were improved; in many of the early trials investigating radiation therapy, a statistically significant percentage of the patients died of radiation-related normal tissue injuries *(7).* One serious potential risk of radiation therapy for breast cancer is symptomatic radiation pneumonitis. Fortunately, with modern irradiation techniques, the risk of radiation pneumonitis is low (<5%), and its course is usually self-limited *(8).*

However, the risk of radiation pneumonitis has recently become a greater clinical concern because of reports suggesting that this risk may increase in patients who receive taxanes. For example, Taghian et al. *(9)* reported that patients with breast cancer who were treated with concurrent or sequential adjuvant paclitaxel-based chemotherapy and radiation therapy had a statistically significant increase in the risk of radiation pneumonitis, compared with patients who received radiation therapy and chemotherapy without paclitaxel (14.6% and 0.9%, respectively, $P<.001$). These data are consistent with an earlier small study that reported a risk of radiation pneumonitis of 25% in 20 patients who received concurrent paclitaxel and radiation therapy *(10).*

It is clear that additional studies are required to determine the risk of developing radiation pneumonitis associated with modern radiation therapy techniques. To date, studies investigating the effect of radiation and taxanes on the development of radiation pneumonitis have included only a small number of patients who often were not receiving treatment on clinical protocols. Therefore, the objective of our study was to elucidate the risk of radiation pneumonitis in patients with breast cancer treated with sequential paclitaxel and irradiation. We analyzed cases of radiation pneumonitis in a group of patients receiving treatment in a prospective phase III institutional randomized trial that compared the efficacy of paclitaxel and 5-fluorouracil–doxorubicin–cyclophosphamide (FAC) treatment with that of FAC only treatment. All patients received the same number of chemotherapy cycles, and the two patient populations were relatively homogenous.

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Patients and Methods

Patients

From May 1, 1994, through June 30, 1998, 524 patients with T1-3 N0-1 breast cancer (which included primary tumors up to 5 cm in size and metastasis to movable axillary lymph nodes) were entered on a prospective phase III trial at The University of Texas M. D. Anderson Cancer Center and randomly assigned to receive either eight courses of FAC or four courses of paclitaxel followed by four courses of FAC. The trial permitted the chemotherapy to be given in neoadjuvant or adjuvant regimens. The M. D. Anderson Cancer Center Surveillance Committee (Institutional Review Board) approved this randomized trial, and all participants signed informed consent before enrollment. In addition, the Surveillance Committee approved a retrospective review of the patients' medical records and radiographs for this study.

The patients' characteristics and treatment outcomes have been reported previously *(11)*. Because radiation pneumonitis can be affected by a variety of radiation therapy parameters, we elected to include only patients who underwent irradiation at our institution. This criterion left 189 patients for our study population (100 in the paclitaxel–FAC group and 89 in the FAC group). The characteristics of these patients according to the two chemotherapy regimens used are summarized in Table 1.

Treatments

Patients randomly assigned to the paclitaxel–FAC group received four cycles of paclitaxel (250 mg/m^2 over a 24-hour continuous infusion every 3 weeks) followed by four cycles of FAC (5-fluorouracil at 500 mg/m^2, doxorubicin at 50 mg/m^2, and cyclophosphamide at 500 mg/m^2 every 3 weeks). Patients randomly assigned to the FAC group received eight cycles of FAC. As shown in Table 1, 79 patients received the first four cycles as neoadjuvant chemotherapy and the subsequent four cycles after surgery. The 110 remaining patients received all eight cycles as adjuvant chemotherapy. All but one patient completed their chemotherapy regimens and underwent surgery before the initiation of radiation therapy. The type of surgery, which was dictated by the extent and location of the tumor and by patient preferences, consisted of breast conservation in 58% of the patients and mastectomy in 42% (Table 2).

Table 1. Patient demographics by chemotherapy group*

Characteristics	FAC group (n = 89)	Paclitaxel–FAC group (n = 100)
Chemotherapy, No. of patients (%)		
Neoadjuvant	33 (37.1)	46 (46.0)
Adjuvant	56 (62.9)	54 (54.0)
Age		
Mean age, y	49.5	48.1
<50, No. of patients (%)	49 (55.1)	55 (55.0)
≥50, No. of patients (%)	40 (44.9)	45 (45.0)
Comorbid illness, No. of patients (%)	13 (14.6)	11 (11.0)
Smoking use, No. of patients (%)		
Any history	31 (34.8)	26 (26.0)
Current	13 (14.6)	9 (9.0)
Tamoxifen use, No. of patients (%)	44 (49.4)	44 (44.0)

*FAC = 5-fluorouracil, doxorubicin, cyclophosphamide.

In all cases, radiation therapy was delivered via a linear accelerator with photons of 6 MV or more or with electrons with various megavoltage energy levels. Four radiation oncologists who specialized in treatment of breast cancer designed the treatment fields. Among this group of physicians, there was consensus with respect to the field arrangements according to specific clinical circumstances. All treatment plans and field designs were prospectively reviewed in a quality assurance meeting. In patients who underwent mastectomy, a four-field technique was typically used to irradiate the chest wall, supraclavicular fossa/axillary apex (SCV), and internal mammary lymph node chain. This technique usually matched an electron field for the medial chest wall/internal mammary lymph node chain with a photon tangential set of fields for the lateral chest wall and a separate anterior field for the SCV. In patients who underwent breast conservation, the breast was irradiated with the use of opposed tangential fields with or without a matched SCV field. The lung volume within the tangential fields was typically limited to less than 2 cm of central lung distance in the tangential treatment field.

Table 2 shows the radiation fields in the patients according to chemotherapy group. The radiation therapy techniques and doses were comparable in the two groups. Among the total of 189 patients, 110 (58%) patients underwent irradiation of the whole breast as part of breast conservation, and 79 (42%) underwent irradiation of the chest wall after mastectomy. Six patients underwent breast reconstruction or implantation before chest-wall irradiation. The majority of the patients in the two chemotherapy groups received irradiation of a third SCV field. The median prescribed radiation dose delivered to the breast or chest wall and regional lymph nodes was 50 Gy; the boost delivered to the tumor bed or chest wall was 10 Gy.

Pneumonitis

All patient charts were retrospectively reviewed for pulmonary symptoms. The symptoms were graded according to a modified radiation pneumonitis toxicity score as defined by the Radiation Therapy Oncology Group toxicity criteria. Because we were specifically interested in the rate of clinically evident pulmonary symptoms that were associated with radiation therapy, patients with asymptomatic radiographic changes were only scored as having radiographic changes, as described below. To increase the sensitivity of detection of mild pulmonary symptoms, we also recorded any pulmonary symptoms that developed after the initiation of radiation therapy. We scored pulmonary symptoms on the following scale: 3 = hospitalization was required; 2 = medication was required; 1 = for all other symptoms.

To further study the effects of treatment on the lungs, we compared chest x-rays taken before irradiation with those taken less than 10 months after radiation therapy and with those taken 10–24 months after radiation therapy. A radiologist who was blinded to the type of treatment the patients received retrospectively reviewed all chest x-rays. Changes in the chest x-rays were subjectively graded, according to both the intensity and extent of the changes, using a severity scale of none, mild, moderate, and marked for scoring.

Statistical Analyses

Univariate analyses of crude rates comparing the development of radiation pneumonitis, pulmonary symptoms, and ra-

Table 2. Radiation fields and doses by chemotherapy group*

Radiation target	FAC group (n = 89)		Paclitaxel–FAC group (n = 100)	
	No. of patients (%)	Dose, Gy (SD, range)	No. of patients (%)	Dose, Gy (SD, range)
Whole breast	54 (60.7)	50.0 (0.0, 50–50)	56 (56.0)	50.1 (0.5, 50–54)
Chest wall	35 (39.3)	49.9 (0.7, 46–50)	44 (44.0)	49.9 (0.9, 44–50)
SCV/axillary apex	64 (71.9)	49.9 (0.6, 46–50)	74 (74.0)	50.0 (0.0, 50–50)
IMC	32 (36.0)	50.0 (0.0, 50–50)	46 (46.0)	50.2 (1.2, 50–58)
PAB	23 (25.8)	43.4 (8.3, 10–50)	28 (28.0)	43.2 (4.1, 40–50)

*FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; SD = standard deviation; SCV = supraclavicular; IMC = internal mammary lymph node chain; PAB = posterior axillary boost.

diographic changes in the two chemotherapy groups were performed with the chi-square test or Fisher's exact test. The actuarial rates of clinically relevant pneumonitis were assessed by use of the Kaplan–Meier method and compared with a log-rank test; patients were censored at death, at time of first recurrence, or at last follow-up examination. Because pulmonary effects can potentially begin after the first radiation treatment, the radiation start date was used to calculate the time intervals for radiation pneumonitis and chest x-ray changes. Because the chest x-ray findings were reviewed at defined intervals after radiation therapy (less than 10 months and 10–24 months), only crude rates were analyzed. In addition, the radiographic changes found during early and late intervals were grouped together for analysis. Two-sided confidence intervals (CIs) for the differences between the comparison groups were provided. Finally, multivariable analysis was performed by use of a logistic regression model that generated odd ratios (ORs) and 95% confidence intervals. All statistical tests were two-sided, and *P* values of less than .05 were considered statistically significant.

Results

Of the 189 patients whose records were reviewed, 100 patients had been randomly assigned to the paclitaxel–FAC arm, and 89 had been randomly assigned to the FAC arm. The median follow-up in the surviving patients was 49.2 months. Patient characteristics in the two groups were comparable (Table 1). The age distribution in the two groups was the same. A similar percentage of patients in the two groups received tamoxifen, but a slightly higher percentage of patients in paclitaxel–FAC group received neoadjuvant chemotherapy.

Radiation Pneumonitis

No difference in the rate of clinically evident radiation pneumonitis was observed between the two study groups. A total of 5.0% of the patients in the paclitaxel–FAC group had clinically evident radiation pneumonitis compared with 4.5% of the patients in the FAC group (difference = 0.5%; 95% CI = –6.6% to 5.5%; $P = 1.00$; Table 3). Only two of the study patients, both in the paclitaxel–FAC group, had to take an oral steroid medication for radiation pneumonitis, and only one patient in the FAC group had to take a narcotic for pulmonary symptoms. None of the patients was hospitalized or died of radiation pneumonitis. The median time to development of radiation pneumonitis was 2.7 months overall (2.7 months for the paclitaxel–FAC group versus 2.5 months for the FAC group), with the earliest at less than 1 month and the latest at 12 months. Because the median follow-up duration was much longer than the median time to development of radiation pneumonitis, the 5-year actuarial rates of radiation pneumonitis were similar to the crude rates in the two chemotherapy groups: 5.1% in the paclitaxel–FAC group and 4.6% in the FAC group (difference = 0.5%, 95% CI = –14.7% to 8.3%; $P = .860$). The radiation fields and chemotherapy regimen received by the patients who developed radiation pneumonitis are shown in Table 3.

Table 4 shows the number of patients in whom any pulmonary symptoms developed during follow-up. A total of 44 patients experienced pulmonary symptoms between the start of radiation therapy and the time to disease recurrence or last follow-up; the majority of these symptoms were probably unrelated to radiation therapy. Of these patients, eight in the pacli-

Table 3. Treatment field arrangement and chemotherapy regimen received by patients who developed clinically evident radiation pneumonitis

Patient	RP grade*	Chemotherapy†	Interval, days‡	Surgical type§	Radiation target(s)‖	Tamoxifen
1	1	Adj-FAC	28	BCT	B	No
2	1	Adj-FAC	26	MRM	CSIP	Yes
3	1	Adj-FAC	40	BCT	BSIP	No
4	2	Neo-FAC	52	MRM	CSI	No
5	1	Adj-P–FAC	35	BCT	BS	No
6	1	Adj-P–FAC	50	BCT	B	No
7	1	Neo-P–FAC	25	MRM	CSI	No
8	3	Adj-P–FAC	85	MRM	CSP	Yes
9	3	Adj-P–FAC	59	BCT	BSIP	Yes

*RP, radiation pneumonitis grade (symptomatic Radiation Therapy Oncology Group toxicity criteria).
†Adj = adjuvant; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; Neo = neoadjuvant; P–FAC = paclitaxel–FAC group.
‡Time interval from the end of chemotherapy to the beginning of radiation treatment.
§BCT = breast-conserving therapy; MRM = modified radical mastectomy.
‖B = breast; C = chest wall; S = supraclavicular; I = internal mammary chain; P = posterior axillary boost.

Table 4. Pulmonary toxicity rates according to the chemotherapy group*

Pulmonary toxicity scale	FAC group (n = 89)	Paclitaxel–FAC group (n = 100)
RTOG grade, No. of patients		
0	85	95
1 or 2	4	3
3	0	2
4	0	0
Crude rate, %†	4.5	5.0‡
Any symptom grade, No. of patients		
0	65	80
1 (no Rx)	14	12
2 (Rx)	10	8
3 (hosp)	0	0
Crude rate, %†	27.0	20.0‡

*FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; RTOG = Radiation Therapy Oncology Group; Rx = medication required; hosp = hospitalization required.

†Crude rate = number of patients with symptoms divided by total number of patients for each group.

‡P = not statistically significantly different from FAC group.

taxel–FAC group and 10 in the FAC group had to take medications, usually antibiotics and antitussives, for their symptoms. None of the patients had to be hospitalized for pulmonary symptoms. The median time to any pulmonary symptoms was 4.4 months for the paclitaxel–FAC group and 3.6 months for the FAC group. The 5-year actuarial rate for development of any pulmonary symptoms was 20.8% (95% CI = 12.3% to 29.3%) for the paclitaxel–FAC and 27.7% (95% CI = 17.8% to 37.6%) for the FAC-alone group (P = .247). During the first 10 months after radiation therapy, 12.0% (95% CI = 6.4% to 20.0%) of the paclitaxel–FAC group and 19.1% (95% CI = 11.5% to 28.8%) of the FAC group developed some pulmonary symptoms, and after the first 10 months, an additional 8% (95% CI = 3.5% to 15.2%) of the paclitaxel–FAC group and 7.9% (95% CI = 3.2% to 15.5%) of the FAC group exhibited pulmonary symptoms.

Unexplained chest pain developed in some of the patients during or after radiation therapy. A total of nine patients had chest pain alone, and 10 patients had chest pain with some pulmonary symptoms. It is of interest that the incidence of chest pain was statistically significantly higher in patients with radiation pneumonitis (33.3%) than in patients who did not have radiation pneumonitis (8.9%) (P = .049).

Patients receiving irradiation of the SCV and internal mammary lymph node chain in addition to the breast or chest wall did not have a statistically significantly higher rate of clinical radiation pneumonitis or any other pulmonary symptoms (Table 5). However, more patients who received irradiation of the SCV used medications for pulmonary symptoms (12.3% versus 2.0%; difference = 10.3%, 95% CI = −0.47% to 18.4%; P = .047). The pneumonitis rate was 3.4% in the patients who received tamoxifen and 6.2% in those who did not receive tamoxifen (difference = 2.8%, 95% CI = −4.8% to 8.0%; P = .482). The sequencing of surgery and chemotherapy did not predict for radiation pneumonitis or any pulmonary symptom development; the pneumonitis rate was 2.5% in the neoadjuvant chemotherapy patients and 6.4% in the adjuvantly treated patients (difference = 3.9%, 95% CI = –3.3% to 9.0%; P = .308). There also was no difference in these rates when the two chemotherapy groups were analyzed separately. Other patient characteristics, such as age, smoking history, and comorbid illnesses, were not associated with the development of clinical radiation pneumonitis or other pulmonary symptoms.

Table 5. Rates of radiation pneumonitis* and chest x-ray abnormalities according to chemotherapy group for different treated radiation field

Radiation target	Radiation pneumonitis, % of patients		Any chest x-ray changes, % of patients	
	FAC	Paclitaxel–FAC	FAC	Paclitaxel–FAC
Chest wall	5.7	4.5	26.7	46.3
SCV/axillary apex	4.7	5.4	29.1	46.8†
IMC	9.4	4.3	28.6	47.6
PAB	8.7	7.1	28.6	53.8

*FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; SCV, supraclavicular; IMC = internal mammary lymph node chain; PAB = posterior axillary boost.

†P = .050; all other comparisons were not statistically significant.

Radiographic Changes

Chest x-rays for 163 patients were available for review. Changes were observed on chest x-rays from 51 patients (31.9%, 95% CI = 24.7% to 39.7%). Radiographic changes were found more often in the paclitaxel–FAC group (39.3%) than in the FAC group (23.7%; difference = 15.6%, 95% CI = −0.11% to 28.8%; P = .034) (Table 6). Furthermore, chest x-ray changes of every grade of severity were more common in patients in the paclitaxel–FAC group than in the FAC group. However, the difference in the rate of moderate to marked chest x-ray abnormalities between the two groups was not statistically significant (9.5% in the paclitaxel–FAC group versus 5.3% in the FAC group; difference = 4.2%, 95% CI = –5.2% to 11.1%; P = .307). To examine the relationship between time after radiation therapy and the radiographic changes, data for initial 10-month (early) period were compared with data for the 10- to 24-month (late) period (Table 7). We found that statistically significantly more changes in chest x-rays occurred in the initial 10-month period after radiation therapy, that is, paclitaxel-treated patients exhibited statistically higher rates of chest x-ray changes during the early interval (P = .038) but not during the late interval (P = .461).

Timing of chemotherapy (neoadjuvant or adjuvant) was not associated with the development of any chest x-ray change (P =

Table 6. Chest x-ray abnormalities after irradiation according to chemotherapy group and irradiation of the supraclavicular field*

Chest x-ray score, No. of patients	Chemotherapy		SCV field	
	FAC group (n = 76)	Paclitaxel–FAC group (n = 84)	No (n = 43)	Yes (n = 117)
Mild	14	25	6	33
Moderate	2	5	0	7
Marked	2	3	0	5
Total	18	33	6	45
Crude rate, %†	23.7	39.3‡	14.0	38.5§

*SCV = supraclavicular; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide.

†Crude rate = number of patients with chest x-ray changes divided by total number of patients for each group.

‡P = .034 (paclitaxel–FAC group versus FAC-alone group).

§P = .003 (treatment of SCV field versus no treatment of SCV field).

Table 7. Chest x-ray abnormalities early or late after irradiation according to chemotherapy group*

Chest x-ray score, No. of patients	Early		Late	
	FAC group (n = 70)	Paclitaxel–FAC group (n = 74)	FAC group (n = 62)	Paclitaxel–FAC group (n = 64)
Mild	10	18	9	13
Moderate	1	4	3	4
Marked	2	3	1	0
Total	13	25	13	17
Crude rate, %	18.6	33.8†	21.0	26.6‡

*Chest x-ray score was based on intensity and extent of changes using a severity scale of none, mild, moderate, and marked. Crude rate = number of patients with chest x-ray changes divided by total number of patients for each group. FAC = 5-fluorouracil, doxorubicin, cyclophosphamide.

†P = .038 for early period, paclitaxel–FAC group versus FAC-alone group.

‡P = .461 for late period, paclitaxel–FAC group versus FAC-alone group.

.379). However, patients who received adjuvant chemotherapy more frequently developed a marked change in their chest x-rays than those who received neoadjuvant therapy (5.3% in the adjuvant group versus 0.0% in the neoadjuvant group; difference = 5.3%, 95% CI = –1.5% to 9.5%; P = .078). Irradiation of the SCV field was the only other factor that was statistically significantly associated with the occurrence of all chest x-ray changes (P = .003; Table 6). Within the subgroup of 120 patients who underwent irradiation of the SCV field, those with chest x-ray changes were observed statistically significantly more often in the paclitaxel–FAC group (46.8%) than in the FAC group (29.1%; difference = 17.7%, 95% CI = –1.7% to 33.6%; P = .050; Table 5). Among the patients who did not undergo irradiation of the SCV field, no difference was observed in the occurrence of chest x-ray changes according to type of chemotherapy (P = .664). Tamoxifen use was associated with a higher rate of any chest x-ray changes (35.1% in the tamoxifen group versus 27.9% in the no tamoxifen group; difference = 7.2%, 95% CI = –9.5% to 21.1%; P = .357), but not statistically significantly so. Other factors, such as smoking, co-morbid illness, and age, were not statistically significantly associated with chest x-ray changes. Treatment with a posterior axillary boost field was not associated with the development of a chest x-ray change overall but was associated with an increased rate of moderate to marked change as represented by a considerable increase in opacification within the irradiated volume (22.2% with a posterior axillary boost field versus 1.7% with no posterior axillary boost field; difference = 20.5%, 95% CI = 9.9% to 28.0%; P<.001). In a multivariable logistic regression analysis, irradiation of the SCV field (OR = 4.3, 95% CI = 1.7 to 11.0; P = .003) and administration of paclitaxel and FAC (OR = 2.1, 95% CI = 1.1 to 4.2; P = .035) independently predicted the development of any chest x-ray changes after radiation therapy.

Discussion

In contrast with previously reported small, uncontrolled studies, we found that sequential treatment with paclitaxel, FAC, and irradiation did not increase the risk of clinically evident radiation pneumonitis compared with treatment with FAC alone followed by radiation therapy. Overall, the incidence of clinically relevant radiation pneumonitis was very low. None of the patients had to be hospitalized or died as a result of radiation pneumonitis. Because the patients in this study received treatment as part of a prospective randomized trial, we were able to compare the rates of radiation pneumonitis in two homogenous groups that differed only in the chemotherapy regimen received. To our knowledge, this is the first reported study to examine the effect of taxane-based chemotherapy on radiation pneumonitis in a randomized group of patients.

To further examine whether the use of taxanes was associated with an increased occurrence of mild symptoms that may not meet the strict Radiation Therapy Oncology Group–defined pulmonary toxicity criteria, we also examined all reported pulmonary symptoms from start of radiation to the date of last follow-up or first recurrence. When interpreting these data, it is important to recognize that the majority of these symptoms were likely unrelated to the treatment and often were only minor upper respiratory tract infections. Using this broad end point, we again found no evidence of an association between use of paclitaxel chemotherapy and an increased rate of pulmonary injury. These data confirm data from previously published small studies that observed no pulmonary toxicities in breast cancer patients treated with radiation and taxane chemotherapy *(12,13)*.

The results of this study are particularly important in that they reassure oncologists that breast cancer can be safely treated with sequential taxane- and anthracycline-based chemotherapy regimens followed by radiation. The initial studies that reported high rates of radiation pneumonitis associated with taxane use had the potential to cause clinicians to avoid the use of either taxane or adjuvant radiation therapy. Because both of these treatments have the potential to increase survival in properly selected patients, our data provide evidence that both treatments can be given sequentially without a concern for potential interactions that could result in a serious pulmonary complication.

As noted above, the data from this study contrast with that from past reports that found high rates of radiation pneumonitis in patients with breast cancer who received paclitaxel either sequentially or concurrently with adjuvant radiation therapy *(9,11)*. In a retrospective review of 41 patients, Taghian et al. *(9)* reported that clinical radiation pneumonitis developed in six patients (14.6%). This rate was statistically significantly higher than that in their historical controls (0.9%) who received adjuvant radiation and chemotherapy without paclitaxel. A number of factors may have contributed to the difference in radiation pneumonitis incidence between our study and theirs. First, in their study, the number of patients was small, and there were only six pulmonary events possibly related to taxane use. Second, the radiation treatment technique used in their study differed from that in our study, which could result in a different total volume of lung irradiated and thus different sensitivity to taxanes. Third, unlike in our study, the chemotherapy schedule and dose of both doxorubicin and paclitaxel varied in patients studied by Taghian et al. Some of their patients received treatment every 3 weeks, whereas others were treated weekly. Finally, and perhaps most important, paclitaxel was given either just before or concurrently with radiation therapy. Hanna et al. *(10)* also found a high rate of radiation pneumonitis with concurrent paclitaxel-based chemotherapy and radiation therapy. A major difference in our study and these two studies *(9,10)* is that the patients who received paclitaxel had an extended interval of 3–4 months between the end of paclitaxel treatment and the initiation of radiation therapy that may have diminished any potential interactions.

Unlike previous reports *(8,14–15),* we did not find an association between the development of radiation pneumonitis with the use of tamoxifen or the addition of SCV radiation. This result may be a reflection of low number of pneumonitis events in our population. However, irradiation of regional lymphatics in the SCV field was associated with chest x-ray changes, and the addition of a posterior axillary boost field was associated with a higher grade of radiographic changes. Although we found no evidence that paclitaxel use was associated with an increased rate of clinically relevant pulmonary injuries, we did find that lung abnormalities on chest x-rays after treatment were more often associated with paclitaxel–FAC use than with FAC use. Using a multivariable model, we found that the use of paclitaxel and irradiation of the SCV field were independently associated with the occurrence of chest x-ray abnormalities. In a subset analysis, we found that the occurrence of chest x-ray abnormalities was statistically significantly greater with paclitaxel use only in patients who underwent irradiation of regional lymph nodes in the SCV field. It is possible that the interaction between paclitaxel and radiation therapy that caused lung damage was relatively weak, so that treatment of a larger lung volume may be necessary for the effect to be observed. Therefore, an association between paclitaxel therapy and radiation-induced lung damage may be more evident in patients who have preexisting lung dysfunction and require irradiation of the regional lymphatics.

In conclusion, the overall risk of radiation pneumonitis appeared to be very low in patients who received chemotherapy followed by radiation therapy and was not affected by the use of paclitaxel. For patients who are to receive sequential chemotherapy and radiation therapy, recommendations for radiation therapy and paclitaxel treatment should not be affected by concerns about the risk of radiation pneumonitis. However, the association between the risk of radiation pneumonitis and the combination of paclitaxel chemotherapy and radiation therapy given either concurrently or close in temporal proximity still needs to be clarified.

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Notes

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