

Lung Dose-Volume Parameters and the Risk of Pneumonitis for Patients Treated With Accelerated Partial-Breast Irradiation Using Three-Dimensional Conformal Radiotherapy

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ABSTRACT

Purpose

There are no data on how complication rates after accelerated partial-breast irradiation delivered by three-dimensional conformal radiotherapy are affected by treatment technique. We therefore examined the risk of pneumonitis in relation to lung dose-volume parameters.

Patients and Methods

Our prospective dose-escalation trial enrolled 198 treated patients from 2003 to 2007. Patients received 32 or 36 Gy in 4-Gy fractions, given twice daily: 29 (14%) were treated with pure photons; 149 (77%) with mixed photons and electrons; and 20 (10%) with protons.

Results

There were four cases of pneumonitis at 4, 4, 7, and 9 months after treatment. All were in the 36-Gy cohort and were treated with pure photons. The risk of pneumonitis for the two cohorts combined was: 17% (four of 24) for an ipsilateral lung volume (ILV) receiving 20 Gy or higher (ILV, 20 Gy) of 3% or higher ($P = .0002$ for comparison to ILV 20 Gy < 3%, Fisher's exact test); 20% (four of 20) for an ILV 10 Gy of 10% or higher ($P = .0001$); and 15% (four of 26) for an ILV 5 Gy of 20% or higher ($P = .0002$).

Conclusion

The risk of pneumonitis appeared related to the ILV treated. This volume can be reduced by using mixed photons and electron when possible. We recommend that the ILV 20 Gy should be lower than 3%, the ILV 10 Gy lower than 10%, and the ILV 5 Gy lower than 20% when purely coplanar techniques are used.

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INTRODUCTION

Patients undergoing breast-conserving therapy (BCT) have traditionally received whole-breast irradiation (WBI). However, most recurrences are at or near the tumor bed.¹ Residual tumor cells in the breast after lumpectomy are confined to a limited area around the index lesion for most patients.^{2,3} Limiting the volume of irradiation might allow BCT to be safely delivered over a much shorter, or accelerated, course, which would make it more convenient for many patients.⁴

Several studies of accelerated partial-breast irradiation (APBI) using interstitial implantation have excellent results with follow-up times in excess of 5 years.^{5,6} The only modern randomized trial comparing APBI to WBI reported to date showed comparable local control and complication rates in both arms.^{7,8} Similar trials in North America and

Europe are currently still enrolling patients or not yet reported.

Three-dimensional conformal radiotherapy (3D-CRT) is an attractive approach for performing APBI. Early results with this modality are favorable.⁹⁻¹³ However, many technical decisions must be made to implement such treatment. These include patient positioning (prone, supine, or lateral decubitus); patient immobilization; assessing the accuracy of patient positioning; movement of the target volume during and between treatments; changes in the size and dimensions of the excision cavity between treatment planning and delivery; the choice of treatment modality (pure photons, mixed photons and electrons, or protons); the number of beams to be used; beam direction; and beam weighting. These choices could well influence the risks of local recurrence or complications.

Radiation pneumonitis is a rare complication of breast radiation therapy, manifested by chronic cough, fever, and nonspecific infiltrates some months after completion of treatment.¹⁴ There have been no reports to date of the risk of such pneumonitis in patients treated with 3D-CRT APBI. This article examines how pulmonary complication rates after 3D-CRT APBI were affected by technique and lung dose-volume parameters for patients treated in a prospective dose-escalation trial. Our findings have implications for what normal-tissue constraints should be used in planning when purely coplanar treatment techniques are used to deliver APBI.

PATIENTS AND METHODS

Protocol Goals, Registration, and Consent

This prospective dose-escalation trial opened to patient entry in September 2003 (Dana-Farber/Harvard Cancer Center protocol 03-179; registry number NCT00694577, clinicaltrials.gov). Its aims were to evaluate the technical feasibility, potential toxicities, and optimal dose for 3D-CRT APBI in selected early-stage female breast cancer patients. Patients gave written informed consent in accordance with institutional and federal requirements. Patients were centrally registered after giving consent and could withdraw at any time.

Patient Selection

Eligibility criteria included: age 18 years or older; Eastern Cooperative Group performance status of 0; infiltrating ductal breast cancer (including tubular, mucinous, and medullary variants) or ductal carcinoma in situ (DCIS) grade 1 or II using the Van Nuys classification¹⁵; radiologic and/or pathologic tumor size 2 cm or smaller; uninvolved nodes or maximum tumor deposit 0.2 mm or smaller on sentinel node biopsy or axillary dissection (if invasive); microscopic tumor margins 2 mm or greater, or no tumor in a re-excision specimen or final shaved margin specimens. Women age 70 years or older with estrogen receptor–positive invasive ductal carcinomas with clinically negative axillary nodes were eligible without pathologic axillary staging if the patient was planning to take hormone therapy. Exclusion criteria included: the presence of lymphovascular invasion or blood vessel invasion; the presence of an extensive intraductal component¹⁶; being a known mutation carrier, including *BRCA1* or *BRCA2*; prior cosmetic or reconstructive breast surgery; psychiatric illness preventing the patient from giving informed consent; medical conditions such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus, or connective tissue diseases which, in the opinion of the treating physician, would make this protocol unreasonably hazardous; pregnancy; or having a currently active second malignancy other than nonmelanoma skin cancers.

Placement of marking clips at the time of tumor excision was encouraged but not mandatory. Pretreatment evaluation with magnetic resonance imaging was also optional.

Treatment

Radiotherapy was required to begin within 4 to 12 weeks from the definitive breast surgery or, if chemotherapy is given first, within 2 to 6 weeks of the completion of chemotherapy. Chemotherapy could not be given concurrently with APBI.

All patients underwent simulation on a dedicated computed tomography (CT) simulator after their agreeing to enter the protocol.¹⁷ Patients were removed from study if the radiation oncologist could not adequately delineate the excision cavity. Formal criteria for determining the extent of the excision cavity were not used. The planning target volume (PTV) was defined by expanding the outlined excision cavity by 1.5 to 2 cm, which was then edited so that it came no closer than 5 mm to the skin surface and was no deeper than the anterior chest wall or pectoralis muscle. (We omitted the intermediate step of explicitly defining a clinical target volume [CTV] as the end result was the same

as that of creating the PTV in two steps.) Additional margin (typically 0.7 cm) was added to create the treatment field borders to account for penumbra.

Patients were treated using 4 Gy fractions given twice daily, with at least 6 hours between fractions, over consecutive days so as to complete treatment within 1 week. Treatment could be started on any day of the week. The first dose-cohort received 32 Gy in 8 fractions, and the second cohort received 36 Gy in 9 fractions. Patients in the third cohort (40 Gy in 10 fractions) are not included in the current article.

Treatment could be given using any combination of photon beams of energy 4 MV or higher, with or without the addition of electrons of any energy, provided the dosimetric requirements of adequately treating the PTV and homogeneity were met. (Examples include mini-tangents plus en-face photons, mini-tangents plus en-face electrons, or wedge-pair photons plus en-face electrons or photons.) Intensity-modulated radiotherapy and proton beam could also be used. A minimum of 3 beams was required, except for proton treatment. Noncoplanar plans were rarely used. Details of proton techniques have been previously described.^{18,19}

Dose was prescribed to the PTV. The dose within the PTV was required to be within 100% to 115% of the prescribed dose, with a change from minimum to maximum within the treatment volume of lower than 15%. All doses were calculated using inhomogeneity corrections. Investigators were encouraged to reduce dose to critical structures as far as reasonably achievable. Plans were approved before the start of treatment by A.R. (for patients treated at Beth Israel Deaconess Medical Center) or A.G.T. or S.N.P. (for patients treated at Massachusetts General Hospital or Boston Medical Center).

Systemic therapy was prescribed at the discretion of the treating physicians. Eight patients (4%) received chemotherapy, with or without hormone therapy, generally before APBI. One hundred thirty patients (66%) received tamoxifen or an aromatase inhibitor. Hormone therapy was generally started after the completion of radiotherapy.

Follow-Up and Toxicity Definition

Patients were to be seen by the treating radiation oncologist 1 to 2 months after the completion of radiation and then every 6 months for the first 5 years, then on an annual basis. At each visit, patients were asked about their symptoms and asked to fill out a questionnaire regarding their impression of the cosmetic results and their overall satisfaction with treatment. The physician completed forms including both oncologic outcome and toxicity. This asked specifically whether the patient had developed radiation pneumonitis and (if present) its severity.

The National Cancer Institute Common Toxicity Criteria for Adverse Events version 3 was used to score toxicity.²⁰ The relevant symptoms for our purposes were: "cough" (grade 1, symptomatic, nonnarcotic medication only indicated; grade 2, symptomatic and narcotic medication indicated; grade 3, symptomatic and significantly interfering with sleep or activities of daily life)(ADL); "dyspnea" (grade 1, dyspnea on exertion, but can walk 1 flight of stairs without stopping; grade 2, dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1 km) without stopping; grade 3, dyspnea interfering with ADL; grade 4, dyspnea at rest or intubation/ventilator required; and "pneumonitis/pulmonary infiltrates" (grade 1, asymptomatic with radiographic findings only; grade 2, symptomatic but not interfering with ADL; grade 3, symptomatic and interfering with ADL, with oxygen indicated; and grade 4, life-threatening with ventilatory support indicated). The degree of toxicity was assessed by the radiation oncologist, based on the patient's reported symptoms, imaging studies, and reports of other treating or consulting physicians (see the case reports in the Appendix, online only).

Statistical Considerations

Dose-volume histograms were examined to determine the ipsilateral lung volume (ILV) receiving a dose of 20 Gy or higher (ILV-20 Gy), 10 Gy or higher (ILV-10 Gy), and 5 Gy or higher (ILV-5 Gy). Similar calculations were performed for the contralateral lung volume. The statistical significance of the relationship of irradiated lung volumes to treatment technique was compared using the two-sided Wilcoxon test.

RESULTS

The trial enrolled 100 patients into each of the first two cohorts between 2003 and 2007 (153 patients from Massachusetts General Hospital, 39 patients from Beth Israel Deaconess Medical Center, and eight patients from Boston Medical Center). Lung dose-volume data were available for 198 treated patients (one patient withdrew consent before treatment, and one was never treated because of an unrelated illness that developed after registration). The median patient age at the time of treatment was 61 years. Eight patients received chemotherapy and 130 either tamoxifen or an aromatase inhibitor.

Twenty-nine patients (14%) were treated with pure photons (16 at 32 Gy, 13 at 36 Gy); 149 patients (77%) with mixed photons-electrons (63 at 32 Gy, 86 at 36 Gy); and 20 (10%) with protons (all at 32 Gy). Patterns of practice varied substantially between the partici-

pating hospitals: 86% of patients were treated with mixed photons-electrons at Massachusetts General Hospital, 32% at Beth Israel Deaconess Medical Center, and 78% at Boston Medical Center.

The median length of follow-up in the first and second cohorts were 38 months (range, 2 to 57 months) and 14 months (range, 1 to 34 months), respectively. Four patients (2%) developed pneumonitis at 4, 4, 7, and 9 months after APBI. All were in the 36-Gy cohort and were treated with pure photons using a 3- or 4-field approach at Beth Israel Deaconess Medical Center. Thus, the incidence of pneumonitis in this particular technique-dose subgroup was 31% (four of 13). The non-tangential fields contributed from 36% to 47% of the total dose at isocenter. Their pulmonary toxicities were scored as grades 3, 2, 1, and 2, respectively.²⁰ The first and fourth patient had bilateral infiltrates most consistent with bronchiolitis obliterans organizing pneumonia, while the other two patients had only ipsilateral infiltrates (some of which were outside the radiation fields) more consistent with classic radiation pneumonitis (Figs 1 and 2). Of interest, the fourth patient eventually developed fibrosis in the directly irradiated lung (Fig 3), although there were no infiltrates in this area at the time she became symptomatic (not shown).

All four patients received prednisone for various durations. The first patient was asymptomatic but still taking prednisone 5 mg daily when last seen at 19 months after the onset of pneumonitis. The other patients were no longer taking steroids but had occasional mild cough at 15, 6, and 9 months, respectively, after the onset of pneumonitis. (Detailed case reports are found in the Appendix).

The distribution of ipsilateral lung dose-volume relationship for all 198 patients is shown in Figure 4. Summary statistics of the ipsilateral and contralateral lung dose-volume relationships in relationship to treatment technique are presented in Tables 1 and 2, respectively. The pure photon technique resulted in increased lung volumes being treated; these differences were statistically significant.

The four patients developing pneumonitis had ILV-20 Gy of 3%, 4%, 6%, and 5%, respectively; their ILV-10 Gy were 13%, 22%, 25%, and 34%; and their ILV-5 Gy were 31%, 45%, 66%, and 54%.

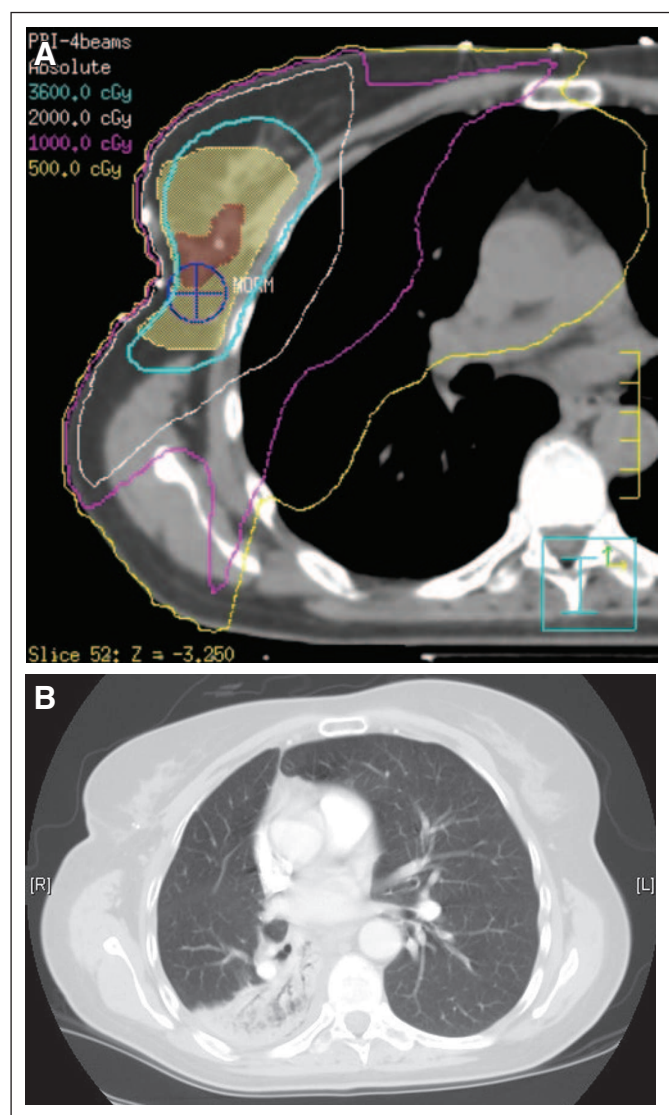


Fig 1. (A) Dose distribution showing 36-Gy (blue), 20-Gy (white), 10-Gy (purple), and 5-Gy (yellow) isodose lines superimposed on planning computed tomography (CT) for patient 1. Brown color-wash, excision cavity; yellow color-wash, planning target volume. (B) Diagnostic chest CT for patient 1 at time of diagnosis of pneumonitis at the same level as Figure 1, showing sparing of the directly irradiated lung. Note the surgical clips marking the excision cavity.



Fig 2. Diagnostic computed tomography for patient 4 at 14 months after completion of radiation therapy, showing persistent fibrotic infiltrates in the treatment area.

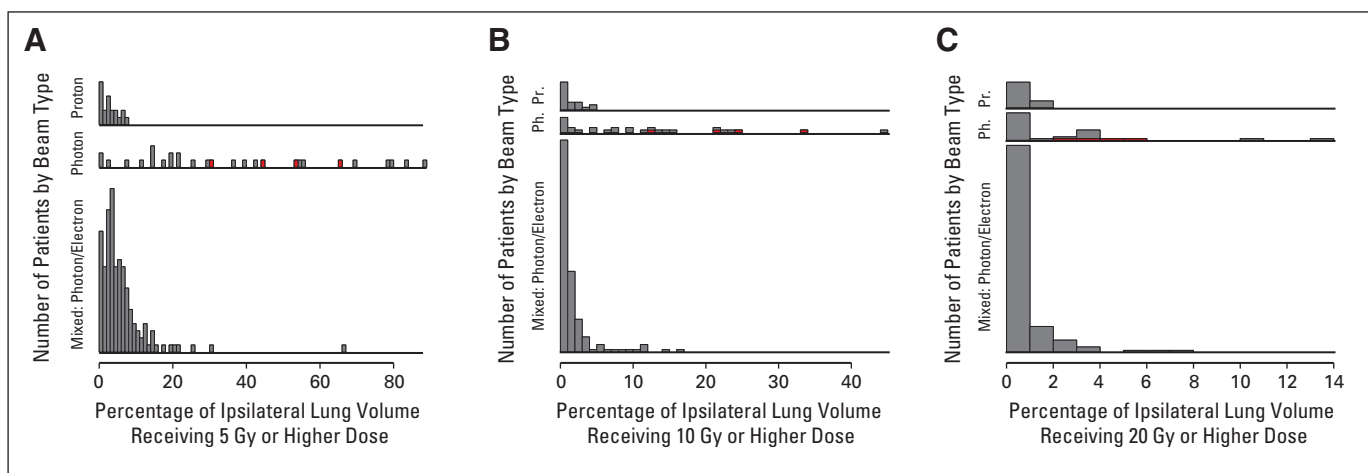


Fig 3. Distribution of ipsilateral lung dose-volumes for study population; patients with pneumonitis highlighted in red. (A) 5 Gy; (B) 10 Gy; (C) 20 Gy. Ph, photons; Pr, protons.

The risk of pneumonitis for the two cohorts combined was: 17% (four of 23) for an ILV-20 Gy of 3% or greater ($P = .0001$ for comparison to ILV-20 Gy < 3%, Fisher's exact test); 20% (four of 20) for an ILV-10 Gy of 10% or greater ($P = .0001$); and 15% (four of 26) for an ILV-5 Gy of 20% or greater ($P = .0002$). There did not appear to be a relation between the contralateral lung volume treated and the risk of pneumonitis (data not shown).

The risk of pneumonitis in the 36 Gy cohort was 36% (four of 11) when 5% of the ILV received a dose of 20 Gy or higher ($P = .0001$ for comparison to ILV-5% less than 20 Gy), 33% (four of 12) when 10% of the ILV received a dose of 10 Gy or higher ($P = .0001$), and 27% (four of 15) when 20% of the ILV received 5 Gy or higher ($P = .0004$).

None of the eight patients receiving chemotherapy developed pulmonary symptoms. The incidence of pneumonitis in patients taking hormone therapy was 1.5% (two of 130), compared to 3% (two of 68) of patients not receiving hormone therapy.

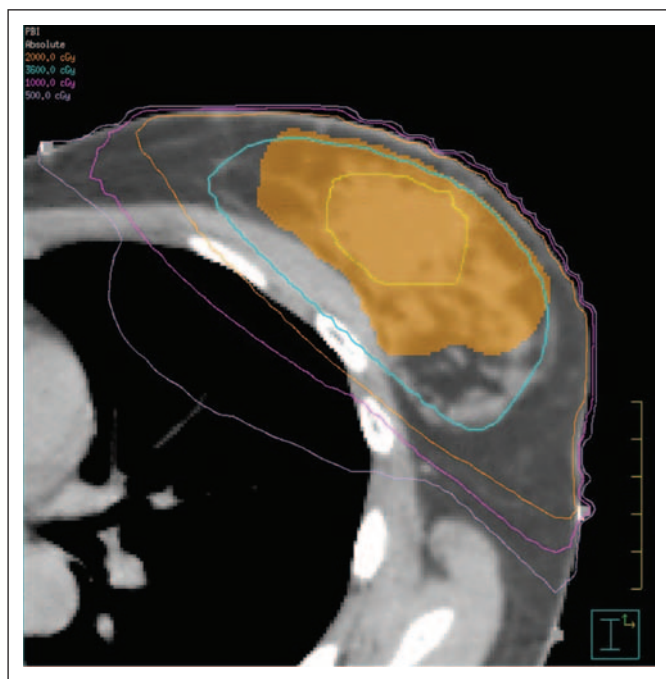


Fig 4. Dose distribution showing 36-Gy (blue), 20-Gy (orange), 10-Gy (purple), and 5-Gy (lavender) isodose lines superimposed on planning computed tomography (CT) for a patient treated with mixed photon-electron technique at Beth Israel Deaconess Medical Center. Yellow line, excision cavity; orange color-wash, planning target volume. The ipsilateral lung volumes were: ipsilateral lung volume (ILV)-20 Gy, 0%; ILV-10 Gy, 2%; and ILV-5 Gy, 11%. The contralateral lung was not exposed.

DISCUSSION

Classic radiation pneumonitis is characterized by chronic cough, fever, and nonspecific infiltrates within the irradiated lung.²¹⁻²³ It generally appears 4 to 9 months after completion of treatment. Its incidence is 1% to 2% after WBI without nodal irradiation.²⁴⁻²⁷ The risk of pneumonitis in patients treated for lung cancers or lymphomas is approximately 5% to 25%.^{22,23,28} Some patients treated with WBI have developed what has been variously termed “bronchiolitis obliterans organizing pneumonia,” “bronchiolitis obliterans with migratory pneumonia,” or “cryptogenic organizing pneumonia.”²⁹ This entity produces the same symptoms as classical radiation pneumonitis, but the infiltrates are wholly or predominantly outside the irradiated area, as illustrated by Figure 2. Two studies from Japan reported an approximately 2% risk in patients treated with WBI.^{30,31} Radiation pneumonitis of either type must be distinguished from interstitial pneumonitis due to other causes.³²

The relationship between lung dose-volumes and the risk of pneumonitis has not been well established for patients treated with WBI. In a study performed at the Harvard Joint Center for Radiation Therapy in Boston, MA, on average 6% of the ILV was treated when the central lung distance was 1.5 cm, 16% when it was 2.5 cm, and 26% when it was 3.5 cm.³³ There was no relationship between the central lung distance and the risk of pneumonitis in patients treated with or without nodal irradiation.²⁴ A study from Duke University found the risk of pneumonitis substantially increased for patients treated with

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Table 1. Ipsilateral Lung Dose-Volume Parameters in Relation to Cohort and Treatment Technique

Group	No. of Patients	Mean Lung Dose (Gy)		%					
		Median	Range	ILV-5 Gy		ILV-10 Gy		ILV-20 Gy	
				Median	Range	Median	Range	Median	Range
All	198	1.4	0-16.2	5.0	0-89.0	1.0	0-45.0	0.0	0-14.0
32-Gy cohort	99	1.4	0-11.0	5.0	0-89.0	2.0	0-45.0	0.4	0-14.0
36-Gy cohort	99	1.4	0.2-16.2	6.0	0-66.0	1.0	0-34.0	0.0	0-7.3
Photons	29	4.0	1.4-16.2	30.0	0-89.0	9.1	0-45.0	1.0	0-14.0
Photons-electrons	149	1.4	0.2-8.6	5.0	0-67.0	1.0	0-17.0	0.0	0-7.3
Protons	20	0.3	0-1.3	3.0	0-8.0	1.0	0-5.0	0.0	0-2.0
Photons, 32 Gy	16	3.7	2-11.0	26.0	0-89.0	5.5	0-45.0	0.0	0-14.0
Photons-electrons, 32 Gy	63	1.4	0.4-6.4	4.0	0-67.0	2.0	0-12.0	1.0	0-5.3
Photons, 36 Gy	13	4.2	1.4-16.2	31.0	8.0-66.0	10.0	1.0-34.0	2.2	0-5.9
Photons-electrons, 36 Gy	86	1.2	0.2-8.6	5.0	0-31.0	1.0	0-17.0	0.0	0-7.3

Abbreviations: ILV, ipsilateral lung volume; ILV-5 Gy, ILV receiving a dose of 5 Gy or higher; ILV-10 Gy, ILV receiving a dose of 10 Gy or higher; ILV-20 Gy, ILV receiving a dose of 20 Gy or higher.

regional nodal irradiation (most of whom also received chemotherapy) when the average lung distance was larger than 3 cm (14%), compared to 2 to 3 cm (6%) or smaller than 2 cm (4%).²⁷ However, there were only three instances of pneumonitis among 319 patients treated with WBI alone, and therefore the effect of the average lung distance was not examined.

To our knowledge, this is the first report concerning the risk of pneumonitis in patients treated with 3D-CRT APBI. It was striking that all four patients who developed pneumonitis were treated with pure photon techniques. This technique exposed a much greater volume of lung to low-dose irradiation than did the mixed photon-electron or proton techniques (Tables 1 and 2 and Fig 4). Nonetheless, the high-dose irradiated volume (20 Gy or higher) was quite small in comparison to that included by standard WBI. It was therefore surprising that such a high rate of pneumonitis was seen. Our findings suggest that relatively low-dose lung irradiation may be of more importance in determining the risk of pneumonitis after irradiation for breast cancer than previously apparent, or that the tolerance of the lung is different when radiation is delivered in 1.8 to 2 Gy fractions given once daily over a 5- to 6-week period than when 4-Gy

fractions are given twice daily over less than 1 week. Data in patients treated for lung cancer suggests that hypofractionation may lower lung tolerance.²³

There were no data to guide us in creating normal-tissue constraints when we designed this protocol. Therefore, we did not incorporate formal guidelines into our trial. The Radiation Therapy Oncology Group (RTOG) trial 0319, conducted from 2003 to 2004, allowed 30% of the prescribed dose of 38.5 Gy (ie, 11.55 Gy) to be given to less than 15% of the ipsilateral lung and 5% of the prescribed dose to less than 10% of the contralateral lung.¹⁰ The current randomized RTOG/National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol 0413/B-39 comparing WBI and APBI has the same ipsilateral lung constraint, but the contralateral lung constraint was changed to allow 5% of the prescribed dose to less than 15% of the contralateral lung.³⁴

Our study has several limitations. Only 29 patients were treated with the en-face pure photon technique, which means the findings in this subgroup may be subject to considerable statistical uncertainty. The dose-volume cut-offs identified for the increased risk of pneumonitis were based on post hoc observation of a small number of events,

Table 2. Contralateral Lung Dose-Volume Parameters in Relation to Cohort and Treatment Technique

Group	No. of Patients	Mean Dose (Gy)		%					
		Median	Range	CLV-5 Gy		CLV-10 Gy		CLV-20 Gy	
				Median	Range	Median	Range	Median	Range
All	198	0.04	0-3.0	0.0	0-39.0	0.0	0-1.0	0.0	0-1.0
32-Gy cohort	99	0.04	0-3.0	0.0	0-39.0	0.0	0-0	0.0	0-0
36-Gy cohort	99	0.05	0-1.3	0.0	0-14.0	0.0	0-1.0	0.0	0-1.0
Photons	29	0.5	0-2.4	0.0	0-17.0	0.0	0-1.0	0.0	0-1.0
Photons-electrons	149	0.04	0-3.0	0.0	0-39.0	0.0	0-0	0.0	0-0
Protons	20	0.0	0-0	0.0	0-0	0.0	0-0	0.0	0-0
Photons, 32 Gy	16	0.5	0-2.4	0.0	0-17.0	0.0	0-0	0.0	0-0
Photons-electrons, 32 Gy	63	0.04	0-3.0	0.0	0-39.0	0.0	0-0	0.0	0-0
Photons, 36 Gy	13	0.3	0.1-1.3	0.0	0-14.0	0.0	0-1.0	0.0	0-1.0
Photons-electrons, 36 Gy	86	0.03	0-0.8	0.0	0-3.0	0.0	0-0	0.0	0-0

Abbreviations: CLV, contralateral lung volume; CLV-5 Gy, CLV receiving a dose of 5 Gy or higher; CLV-10 Gy, CLV receiving a dose of 10 Gy or higher; CLV-20 Gy, CLV receiving a dose of 20 Gy or higher.

and hence we cannot say with certainty that they are the optimal ones. Also, most patients treated with 3D-CRT APBI have been enrolled on the NSABP/RTOG trial or treated according to its guidelines. The NSABP/RTOG trial requires the use of noncoplanar beams that reduce substantially direct exposure of the lung; direct en-face photon fields, such as we used, are not allowed. The NSABP/RTOG trial also has lung dose-volume constraints that our trial did not. Hence, our findings cannot be directly extrapolated to patients treated on the NSABP/RTOG trial.

In summary, the risk of pneumonitis after coplanar-beam 3D-CRT APBI appears related to the ipsilateral lung volumes treated. This volume can be reduced by using mixed photon-electron techniques when possible and avoiding en-face photon beams. Based on these results, we have mandated lung dose-volume guidelines for the third cohort of patients on our protocol (ILV-20 Gy must be kept to < 3%, the ILV-10 Gy to < 10%, and the ILV-5 Gy to < 20%). Patients whose lung dose volumes are lower than these values appear to have a minimal risk of developing pneumonitis. However, these parameters were generated in a small, uniquely treated group of patients and should not be extrapolated to all external-beam partial-breast treatment in general until confirmed by larger trials. Investigators should be cautious not to extrapolate lung tolerance parameters that have been established for conventionally-fractionated WBI experience to APBI. Refinement of normal-tissue constraints will only be achieved through completion and analysis of well-structured clinical trials.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Case Reports

Case 1. This patient was 55 years old at diagnosis of an infiltrating ductal carcinoma of the right breast. She had smoked one pack of cigarettes per day for 30 years until diagnosis. She was treated in May 2006 with a 4-field plan (right medial minitangent 7.5×9.4 cm which contributed 1.28 Gy to the isocenter dose, right lateral minitangent 9.7×9.9 cm for 1.20 Gy, right anterior oblique 10.0×8.4 cm for .60 Gy, and right lateral 8.8×8.4 cm for .92 Gy) using 6 MV photons (Fig 1A). She began tamoxifen 20 mg daily just over 1 month after completing partial-breast irradiation.

She developed cough and fevers with some postnasal drip and rare sputum production in mid-September 2006. Chest x-ray in October 2006 showed right lung infiltrates and volume loss. She was given azithromycin, with decreased cough. She still had dyspnea on exertion to one flight of stairs. Chest computed tomography (CT) showed air-space opacification with air bronchograms in the right upper lobe crossing the major fissure to involve the posterior-superior segment of the right lower lobe, with an adjacent right pleural effusion (Fig 1B). Multiple 3 to 6 mm nodules were seen throughout the lung fields, including the left lower lobe. The lung directly irradiated was entirely spared from these changes, which were diffuse in the remainder of the right lung. Forced vital capacity (FVC) was 2.16 L (64% of predicted) and forced expiratory volume in 1 second (FEV1) was 1.7 L (67%); diffusion measurements were not performed. The overall impression of the consultant pulmonologist was consistent with cryptogenic-organizing pneumonia. She was scored as having grade 3 pulmonary toxicity.

She began prednisone (40 mg daily) with improvement of her cough and dyspnea and resolution of her fevers. Chest CT in November 2006, showed the consolidation, effusion, and infiltrates had nearly entirely resolved. There was some persistent volume loss. She stopped taking steroids entirely soon after. However, she began coughing again in early January 2007. CT showed right upper lobe consolidation with volume loss and air bronchograms and new consolidation of the left lower lobe. She therefore began prednisone 40 mg daily, with rapid resolution of her cough. Prednisone was subsequently tapered. Pulmonary function testing in February 2008 showed FVC of 3.39 L (101%) and FEV1 of 2.5 L (100%). Chest x-ray in April 2008, was unremarkable.

She had no cough, other pulmonary symptoms, or fatigue when last seen in follow-up in May 2008, at which time she was taking prednisone 5 mg daily. Examination was unremarkable.

Case 2. This patient was 54 years old at diagnosis of ductal carcinoma in situ of the left breast. She had a long-standing history of asthma and had smoked in the past but only rarely at diagnosis. She was treated in September 2006 using a 4-field plan (medial minitangent 8.4×11 cm for .80 Gy contribution to the isocenter dose, lateral minitangent 9.6×11 cm for 1.32 Gy, anterior 10.9×10.3 cm for 1.16 Gy, and left anterior oblique 11×10.4 cm for .72 Gy) using 6 MV photons except for the lateral minitangent, which was treated with 10 MV photons. She did not receive adjuvant systemic therapy.

In January 2007, she began having dyspnea on exertion and night sweats but no fevers or cough. Chest CT in February showed multiple areas of focal peripheral and subpleural consolidation, predominantly in the left upper lobe (sparing the lingula) and the superior segment of the left lower lobe, with air bronchograms. There were also small confluent and nodular subpleural opacities medially and in the superior segment of the left upper lobe and posteromedially at the left lung base. The lung within the radiation fields showed fibrotic changes consistent with treatment, but the areas of consolidation were superomedial and posteroinferior to the treatment area. There were no right lung infiltrates. She was scored as having a grade 2 pulmonary toxicity.

She began a 6-day course of prednisone, with rapid but modest improvement in her dyspnea and disappearance of the night sweats. Fiber-optic bronchoscopy in March 2007 showed no abnormalities, with transbronchial lung biopsy showing reactive bronchial epithelial atypia only; other biopsies and pulmonary lavage specimens were unremarkable. Her symptoms resolved entirely after the single course of prednisone, without further episodes. Chest CT in June 2007 showed no infiltrates or adenopathy, with minimal scarring in the area immediately in the treatment field and a linear scar extending from that region toward the hilum.

She was fully active without limitations when most recently seen in follow-up in April 2008. Examination was unremarkable.

At most recent follow-up in April 2008, her cough was still present but reduced in severity.

Case 3. This patient was 42 years old at diagnosis of ductal carcinoma in situ of the right breast. She had no previous pulmonary illnesses but had smoked for a total of 10 pack-years, quitting 12 years before diagnosis. She was treated in April 2006 using a 3-field plan (medial minitangent 10×9.7 cm contributing 1.40 Gy to the isocenter dose, lateral minitangent 10.5×9.7 cm for 1.14 Gy, and right anterior oblique 11.2×9.3 cm for 1.46 Gy) using 6 MV photons. She began tamoxifen on May 1, 2006, but stopped it after 2 weeks due to hot flashes and malaise.

In November 2006, she began having chronic nonproductive coughing. Pulmonary function tests and chest x-rays were normal. She received several courses of systemic steroids and antibiotics with no clear benefit. Chest CT in May 2007 showed subpleural parenchymal opacity in the area of her radiation fields in the lateral inferior right upper lobe, extending to the lateral right middle lobe, and two adjacent right lateral rib fractures. There were no infiltrates elsewhere. She was treated empirically with omeprazole and metoclopramide without benefit. She was scored as having a grade 1 toxicity.

Case 4. This patient was age 69 at the diagnosis of an infiltrating ductal carcinoma of the right breast. She had no lung diseases; she had a 20 pack-year smoking history but had stopped 36 years before. She was treated in December 2006 with a 3-field plan (medial minitangent 11.2×8.3 cm contributing .74 Gy to the isocenter dose, lateral minitangent 11.2×8.3 cm for 1.48 Gy, and right anterior oblique 10.9×8.3 cm for 1.92 Gy) using 6 MV photons. Therefore, 46% of the isocenter dose was given by an en-face field. She began anastrozole in November 2006.

In mid-September 2007, she developed cough and fever to 101°F with some shortness of breath. Chest x-ray in October 2007 showed infiltration in the right middle and right lower lobes. She was placed on erythromycin and prednisone 30 mg daily for 7 days. She seemed to have some symptomatic improvement. CT of the chest in November 2007 showed an approximately 1.9×1.8 cm lesion within the right middle lobe with a surrounding region of ground-glass opacity and scattered areas of ground-glass opacities through both lungs, with peripheral and basilar predominance of interstitial thickening. During November she took another course of erythromycin for 21 days and also was given diflunisal for discomfort with coughing, which she used 2 to 3 times daily. She was given a prescription for a 21-day course of levofloxacin in early December with hydrocodone and ibuprofen used for discomfort intermittently. CT of the chest in December 2007 showed persistent increased density in the right middle lobe with airspace density and air bronchograms and some volume loss, which had improved slightly. There was no longer any associated mass. The patchy airspace densities in the right lower lobe were improved, but there was little change elsewhere. By December 2007 she had intermittent dry cough but no fevers or dyspnea on exertion. Examination showed some inspiratory crackles in the right midposterior lung zone without wheezing. She was scored as having a grade 2 pulmonary complication.

She developed some discomfort in the right anterolateral chest over the winter. Bone scan in February 2008 showed faint activity in the right seventh rib. CT in February 2008 showed two rib fractures in the anterolateral right ribs and an infiltrate in the right middle lung, both findings in the area of her radiation treatment (Fig 2). CT of the chest in April 2008 showed a stable 10×15 mm right middle lobe nodule, surrounding interstitial thickening along the minor fissure, interstitial changes in the right upper lung and to a lesser degree in the left upper lung, and healing rib fractures in the fourth, fifth, and sixth ribs. When seen most recently in June 2008, she had no shortness of breath and only occasional coughing.