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Clinical Investigation: Breast Cancer

Predicting the Risk of Secondary Lung Malignancies Associated With Whole-Breast Radiation Therapy

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Summary

The risk of secondary lung cancers after whole breast irradiation is an important concern for early stage breast cancer patients and their physicians. A novel, biologically-based model was used to quantify and compare the risk for patients planned for supine breast irradiation and for prone breast irradiation. The prone breast technique leads to a substantially lower risk of secondary lung malignancy than treatment with the supine breast technique. Breast radiotherapy techniques may have different associated risks of secondary lung malignancy.

Purpose: The risk of secondary lung malignancy (SLM) is a significant concern for women treated with whole-breast radiation therapy after breast-conserving surgery for early-stage breast cancer. In this study, a biologically based secondary malignancy model was used to quantify the risk of secondary lung malignancies (SLMs) associated with several common methods of delivering whole-breast radiation therapy (RT).

Methods and Materials: Both supine and prone computed tomography simulations of 15 women with early breast cancer were used to generate standard fractionated and hypofractionated whole-breast RT treatment plans for each patient. Dose−volume histograms (DVHs) of the ipsilateral breast and lung were calculated for each patient on each plan. A model of spontaneous and radiation-induced carcinogenesis was used to determine the relative risks of SLMs for the different treatment techniques.

Results: A higher risk of SLMs was predicted for supine breast irradiation when compared with prone breast irradiation for both the standard fractionation and hypofractionation schedules (relative risk [RR] = 2.59, 95% confidence interval (CI) = 2.30−2.88, and RR = 2.68, 95% CI = 2.39−2.98, respectively). No difference in risk of SLMs was noted between standard fractionation and hypofractionation schedules in either the supine position (RR = 1.05, 95% CI = 0.97−1.14) or the prone position (RR = 1.01, 95% CI = 0.88−1.15).

Conclusions: Compared with supine whole-breast irradiation, prone breast irradiation is associated with a significantly lower predicted risk of secondary lung malignancy. In this modeling study, fractionation schedule did not have an impact on the risk of SLMs in women treated with whole-breast RT for early breast cancer. © 2012 Elsevier Inc.

Keywords: Secondary malignancy, Whole-breast irradiation, Prone breast irradiation, Hypofractionation, Early-stage breast cancer

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Introduction

The risk of secondary lung malignancy (SLM) is a significant concern for women treated with whole-breast radiation therapy after breast conserving surgery for early-stage breast cancer. This concern has gained prominence as the use of adjuvant breast radiation has increased and as prognosis has steadily improved over the past decade (1–4). Furthermore, the latency period of radiation-induced second cancers is often greater than 10 years, and the risk persists 30 to 40 years after therapy (5–8). As prospective trials may not be feasible and as epidemiologic studies would require extremely long follow-up, modeling approaches may provide more immediate insight into the magnitude of the potential risks. It would be particularly valuable to comparatively estimate the risk of secondary lung malignancies between two clinically acceptable whole-breast irradiation techniques such as supine whole-breast irradiation, the current standard adjuvant radiotherapy technique, and the clinically accepted alternative techniques of prone breast irradiation and hypofractionated breast irradiation (9–11). A comparative analysis of the risk estimates between these techniques may have an impact on treatment decision making.

In this study, a novel biologically based mathematical model of spontaneous and radiation-induced carcinogenesis (12, 13) was used to quantitatively predict the lifetime absolute and relative risks of secondary lung malignancy for women who were planned for breast radiation treatment in both the standard supine position and the alternative prone position, using both the standard fractionation schedule and the alternative hypofractionated schedule.

Methods and Materials

Patient characteristics

The treatment plans of 15 patients with early-stage breast cancer treated with whole-breast radiotherapy at Columbia University Medical Center (CUMC) were retrospectively assessed in this institutional review board–approved study. All had biopsy-proven breast carcinoma that had been excised with negative margins by breast conserving surgery and had undergone either sentinel node biopsy or axillary node dissection if indicated.

The median patient age was 57 years. Patient characteristics are summarized in Table 1.

Table 1 Patient characteristics

Characteristic	No. of patients	Percentage (%)
Age (y)		
40–49	1	7
50–59	8	53
60–69	4	27
70–79	1	7
80–89	1	7
Breast side		
Left	6	40
Right	9	60
Pathologic stage		
DCIS	5	33
T1N0	9	60
T2N0	1	7
Breast volume (cc) by position		
Prone		
<1,000	6	40
1,001–2,000	7	47
2001–3000	2	13
Mean breast volume: 1,221 cc		
Supine		
<1,000	7	47
1,001–2,000	8	53
2,001–3,000	0	0
Mean breast volume: 1,038 cc		

Abbreviations: cc = cubic centimeters; DCIS = ductal carcinoma *in situ.*

Treatment planning methods

All patients were simulated by computed tomography (CT) for radiotherapy in both the prone and the supine positions. The CT acquisition data included slice thickness of 2.5 mm. CT images were imported into a commercial treatment planning system (Eclipse v.8.1; Varian Medical Systems, Palo Alto, CA) to define both target and nontarget structures. Standard whole-breast treatment plans were designed for each patient in each treatment position. An example of a typical patient treatment plan pair is shown in Figure 1.

The treated breast and ipsilateral lung were contoured for each patient by a single radiation oncologist (J.N.) and reviewed by a second radiation oncologist (R.J.B.). Four plans were generated for each patient ($n = 60$ total plans): a standard fractionation plan in the supine position, a hypofractionated plan in the supine position, a standard fractionation plan in the prone position, and a hypofractionated plan in the prone position. The prescription dose for the standard fractionation schedule was 5,000 cGy in 25 fractions, five fractions weekly. For the hypofractionated schedule, the prescribed dose was 4,256 cGy in 16 fractions (11), five fractions weekly. All plans were normalized so that 95% of the breast target volume received 95% of the prescribed dose. Dose–volume histograms (DVHs) of the target and normal tissues were calculated for each treatment plan. Figure 2 shows a typical matched dose-volume histogram for a patient simulated in both the supine and the prone positions with a standard fractionation schedule and a hypofractionated schedule used for each position.

Differential DVH data for the ipsilateral lung from each treatment plan were then analyzed using a Fortran program that uses a biologically based mathematical model of spontaneous and radiation-induced carcinogenesis (12, 13). In a differential DVH, radiation dose is split into bins of 1 cGy, and corresponding fractional volumes of irradiated tissue are estimated for each bin by the treatment planning software. The model formalism allows the predicted lifetime risk of radiation-induced lung cancer to be estimated for each bin, and these estimates are summed to generate risk predictions for the entire DVH for each plan.

The carcinogenesis model (12, 13) used in the estimation of the risk of SLMs emphasizes the different kinetics of radiation-induced cancer initiation and promotion and tracks the yields of premalignant cells before, during, shortly after, and long after radiation exposure. Briefly, the model integrates analyses of processes that operate during irradiation with those that operate on longer time scales before and after exposure. The model assumes

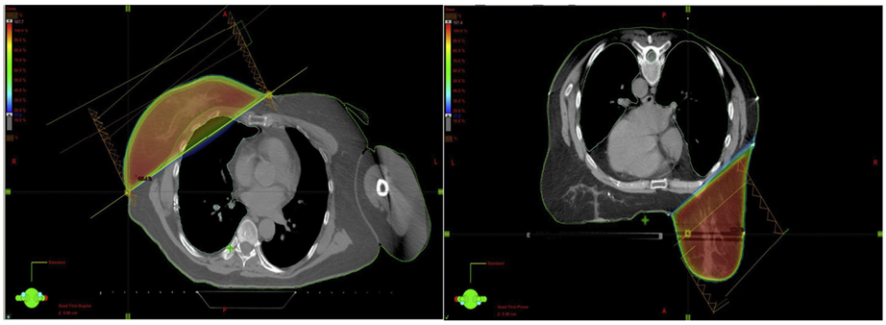

Fig. 1. Sample dose color map of the same patient in the supine (left) and prone (right) positions.

that normal organ-specific stem cells, which reside in compartments generically called niches, can undergo initiation to a premalignant state, either spontaneously or by exposure to ionizing radiation, and can then undergo transformation into fully malignant cells that can eventually form tumors. Radiation is also assumed to have the potential to increase the mean number of premalignant cells per niche (*i.e.*, promotion). In earlier work, this model was shown to reproduce the main dose-dependent features of radiation-induced second cancers after radiotherapy (13, 14).

In addition to the differential DVH data, the model used the following variables for each treatment plan: number of radiotherapy dose fractions, dose per fraction, time gaps between fractions, and age of the patient. Model parameters that pertain to radiation-induced lung cancer risk were transcribed from a previous publication where the same model was used to analyze radiogenic lung cancer risks in Japanese atomic bomb survivors and patients treated with radiotherapy for Hodgkin's disease (13). The parameters that pertain to background lung cancer risk in women were estimated by fitting the model to age-dependent lung cancer incidence data for U.S. women from the Surveillance, Epidemiology, and End Results (SEER) database (15). Survival rates for breast cancer patients as function of time after treatment were calculated by adjusting the life table for U.S. women from the year 2000 census by relative survival data for breast cancer patients obtained from SEER (15).

Model-predicted absolute risks of lung cancer for each year after radiotherapy were adjusted by the probability of the patient to survive up to the given year, and all of these results were summed to obtain lifetime absolute risk. The lifetime absolute risks associated with each plan were averaged and compared with average lifetime absolute risks for individuals of the same age receiving no radiotherapy. This procedure allowed lifetime absolute risks of lung cancer, as well as the relative risks of SLMs of the different treatment techniques, to be estimated.

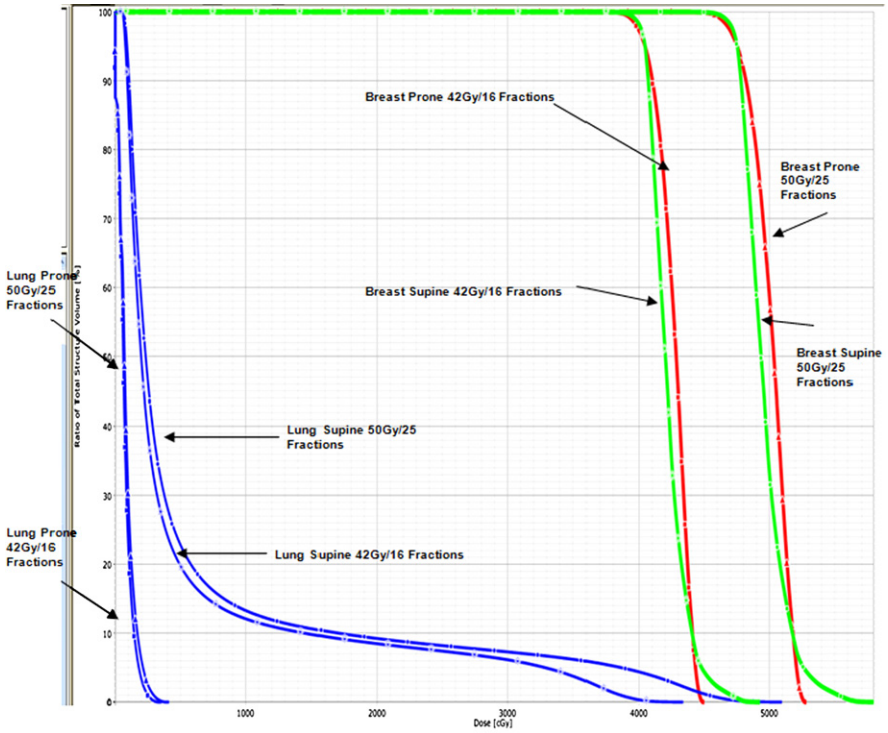

Fig. 2. Sample dose–volume histogram (DVH) of the same patient in the prone and supine positions for both the standard fractionation and hypofractionation schedules.

Results

There was statistically significantly less radiation dose delivered to the ipsilateral lung for each of the 15 patients in the prone position when compared with the supine position. For the standard fractionation schedule of 5,000 cGy in 25 fractions, the average mean lung dose (MLD) was measured to be 54.2 cGy ± 5.2 cGy (standard error [SE]) in the prone position vs. 645.5 cGy ± 43.5 cGy in the supine position ($p < 0.001$, paired t-test). A similar difference in average MLD was noted between the supine and prone hypofractionated plans (548.7 cGy ± 37.3 cGy and 46.1 cGy ± 4.5 cGy, respectively, $p < 0.001$).

The predicted lifetime absolute risks of lung cancer for each patient are shown as a scatter plot for treatment with standard fractionation in both the prone and supine positions in Figure 3. The mean predicted lifetime absolute risk of lung cancer for standard fractionation was 4.86% ± 0.43% in the supine position and 1.99% ± 0.18% in the prone position for a mean difference of 2.87% (95% confidence interval [CI] = 2.28 to 3.47%; $p < 0.001$, paired t-test). An analysis of hypofractionated plans revealed that the mean predicted lifetime absolute risk of lung cancer was 4.78% ± 0.43% in the supine position and 1.88% ± 0.17% in the prone position ($p < 0.001$).

There was no significant difference in lifetime absolute lung cancer risk when comparing the two fractionation schedules for the supine position ($p = 0.18$). The mean difference in absolute risk between the fractionation schedules was 0.10% (95% CI = 0.08−0.13%; $p < 0.001$, paired t-test) in the prone position. However, there was no difference in the relative risk (RR) of SLMs between standard fractionation and hypofractionated schedules in either the supine (relative risk [RR] = 1.05, 95% CI 0.97−1.14) or prone positions (RR = 1.01, 95% CI = 0.88−1.15). A higher risk of SLMs was predicted for supine breast irradiation when compared with prone breast irradiation for both the standard fractionation and hypofractionation schedules (RR = 2.59, 95% confidence interval [CI] = 2.30−2.88, and RR = 2.68, 95% CI = 2.39−2.98, respectively).

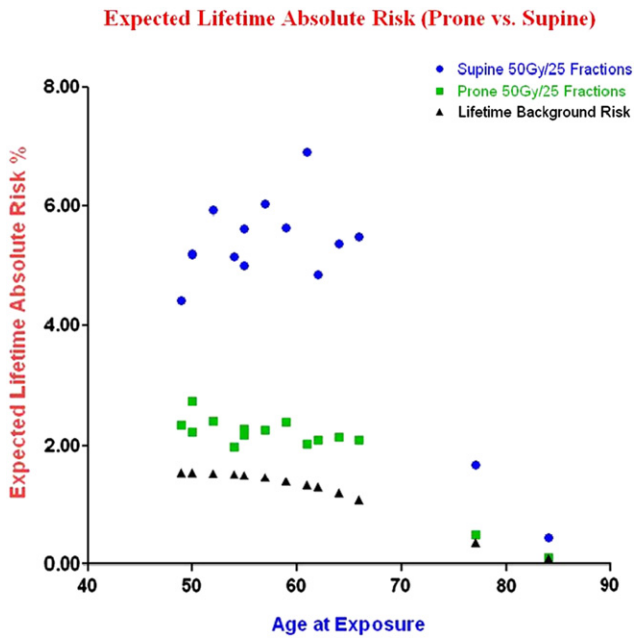

Fig. 3. Predicted lifetime absolute risk of lung malignancy vs. age at exposure, prone (green) vs. supine (blue) breast irradiation for standard fractionation.

Finally, the relative risks of SLMs for the various treatment techniques compared with background risk were as follows: supine standard fractionation, RR = 4.04, 95% CI = 3.62−4.46; supine hypofractionation, RR = 3.98, 95% CI = 3.56−4.40; prone standard fractionation, RR = 1.56, 95% CI = 1.46−1.66; and prone hypofractionation, RR = 1.48, 95% CI = 1.40−1.57. The relative risks compared with background risk by schedule and position are summarized in Table 2.

The mean expected lifetime absolute risks of lung cancer associated with all four treatment techniques and the background risk are shown in Figure 4.

Discussion

Several epidemiological studies with long-term follow-up have documented an increased risk of SLMs in women who have been treated with post-mastectomy radiotherapy (16−20) or supine whole-breast radiotherapy (21−30). These studies have typically included patients treated with standard whole-breast irradiation to a total dose of 4,500 to 5,000 cGy in the supine position (31). This standard of care technique, however, has been known to result in substantial levels of radiation delivered to nearby organs including the ipsilateral lung and the heart (32, 33).

In recent years, alternative techniques of breast irradiation have emerged for patients with early-stage breast cancer. Prone breast irradiation was initially developed to improve dose homogeneity in woman with larger breasts (34). The technique also typically results in decreased dose to normal tissues, including the heart and lungs, as the breast tissue tends to fall away from the chest wall. Many studies have confirmed the improved dosimetric results of prone breast irradiation by showing consistently decreased radiation dose to the lungs (35−39). However, there have been no studies published to date that quantify, or have attempted to quantify, the excess relative risk of secondary lung malignancy when a breast cancer patient is treated with radiotherapy in the supine position compared with the prone position.

Another alternative technique, using a hypofractionated schedule, has been shown to be equivalent to standard fractionated whole-breast RT in a recently updated randomized controlled trial with 10-year median follow-up (11). Because of the relatively recent acceptance of this fractionation schedule, there have been no studies published to date that have quantified, or attempted to quantify, the relative risk of secondary lung malignancy when a breast cancer

Table 2 Lifetime relative risks of SLM by technique

Breast radiation technique	RR (95% CI)
Supine whole-breast radiotherapy (50 Gy/25 fractions)	4.04 (3.62−4.46)
Supine whole-breast radiotherapy (42 Gy/16 fractions)	3.98 (3.56−4.40)
Prone whole-breast radiotherapy (50 Gy/25 fractions)	1.56 (1.46−1.66)
Prone whole-breast radiotherapy (42 Gy/16 fractions)	1.48 (1.40−1.57)
None (background risk)	1.00

Abbreviations: CI = confidence interval; RR = relative risk; SLM = secondary lung malignancy.

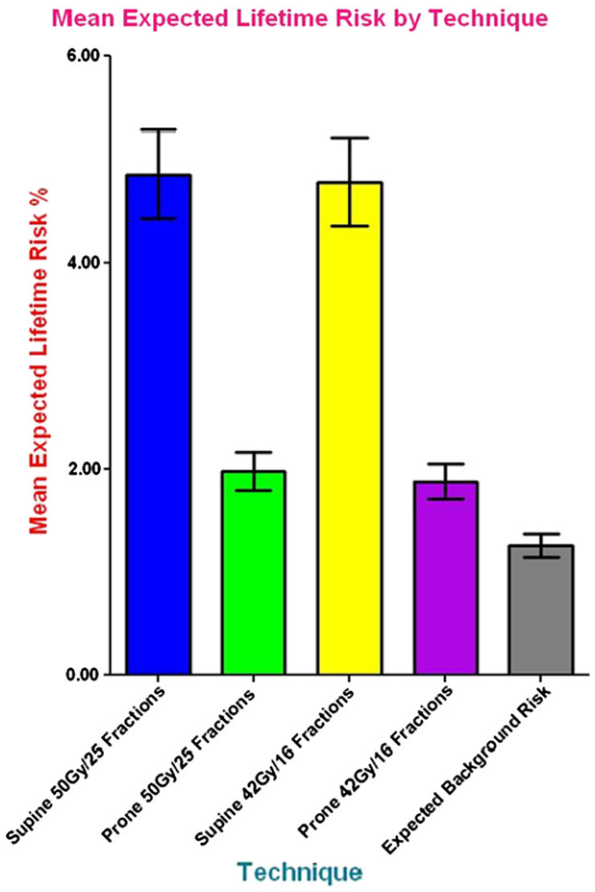

Fig. 4. Mean predicted lifetime absolute risk of lung malignancy by breast irradiation technique. Bars indicate standard errors.

patient is treated with hypofractionated breast radiotherapy compared with standard fractionated breast radiotherapy.

The relative risk estimates for SLMs from the present study are comparable with the relative risks of secondary lung malignancies estimated from several retrospective series on patients treated with supine whole-breast irradiation (21–25). A study from the Institut Curie examined the risk for different secondary malignancies after breast radiotherapy and noted a statistically significant increase for lung cancers (RR = 3.1), a risk that persisted after 10 years of follow-up from radiation treatment (21). In a large cohort study of patients from the Connecticut Tumor Registry, the estimated relative risk of secondary lung malignancy after breast radiotherapy was 2.8 after 15 years of follow-up (22). Another study using the Connecticut Tumor Registry by Neugut *et al.* found a relative risk of 3.2 for secondary lung malignancies after more than 10 years from the initial primary breast cancer (23). A large-scale retrospective SEER analysis on more than 180,000 breast cancer patients treated with radiotherapy estimated the relative risk of SLMs to be 1.93 at 10 years and increasing with longer follow-up (24). A study using the Swedish Cancer Registry to identify 141,000 women with breast cancer estimated the relative risk of SLMs to be 3.2 at 10 years (25). Finally, a separate SEER analysis focusing on mortality showed a long-term increased risk of lung cancer mortality in patients treated with whole-breast RT compared with the general population with a relative risk of 2.7 after 15 years (40).

The current study suggests that the predicted lifetime risk of radiotherapy-induced lung cancer is significantly lower when women are treated in the prone position with whole-breast radiotherapy compared with the more commonly used supine position. According to these estimates, the relative risk of secondary lung malignancies may be decreased more than twofold using the prone breast technique. On the other hand, hypofractionated breast radiotherapy did not appear to clinically significantly affect the secondary lung malignancy risk when compared with standard fractionation for a given treatment position.

There are several limitations that are important to note with respect to the current study. First, this study was performed on a limited number of patients with risk factors that may not be representative of those of the general population. Second, these results are based on a model that, while improved over older secondary malignancy models as it incorporates both short-term and long-term carcinogenic processes, excludes potential confounding factors that may affect secondary lung malignancy risk. These potential factors include family history, chemotherapy use (17), and, most importantly, smoking status (23, 29, 41–43). Third, this study did not investigate the potential influence of either a boost to the tumor bed or the breath-holding technique on the risk of SLMs. The breath-holding technique, which is occasionally used in supine breast radiation therapy and may result in decreased ipsilateral lung dose (44), was not used in any of these patients. Fourth, the amount of lung irradiated in a typical supine breast radiotherapy plan may vary from physician to physician, which may limit the application of these findings. Fifth, prone breast radiation therapy itself has several potential limitations including less reliable setup and patient tolerability as compared with supine positioning (45). Furthermore, prone positioning may not be applicable in patients requiring regional nodal irradiation such as patients with locally advanced or node positive breast cancer (33). Finally, partial breast irradiation, a newer technique currently the subject of a large-scale randomized trial, NSABP B-39 (46), may result in an even lower risk of secondary lung malignancy than prone breast radiation. This topic is currently being studied at our institution in a separate modeling analysis.

Conclusions

Patient position during whole-breast radiation treatment is an important factor in determining the associated risk of secondary lung malignancy. Treatment in the prone position produces a substantially lower risk of secondary lung malignancy than treatment in the more common supine position. Quantifying this risk may be useful for clinicians as they counsel women with early stage breast cancer about their treatment options.

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