International Journal of
Radiation Oncology
biology ● physics

www.redjournal.org

Clinical Investigation: Breast Cancer

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

John Ng, M.D.,* Igor Shuryak, M.D., Ph.D.,† Yanguang Xu, Ph.D.,* K.S. Clifford Chao, M.D.,* David J. Brenner, Ph.D., D.Sc.,† and Ryan J. Burri, M.D.*

**Department of Radiation Oncology, Columbia University Medical Center, New York, NY; and †Center for Radiological Research, Columbia University Medical Center, New York, NY*

Received May 10, 2011, and in revised form Jul 19, 2011. Accepted for publication Sep 19, 2011

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

Reprint requests to: John Ng, M.D., Department of Radiation Oncology, Columbia University Medical Center, 622 West 168th St., New York, NY 10032. Tel: (718) 490-4939; Fax: (212) 305-2141; E-mail: jon9024@nyp.org

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. 1101−1106, 2012

doi:10.1016/j.ijrobp.2011.09.052

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.

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.*

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.

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