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CLINICAL INVESTIGATION **Breast**

REDUCTION OF CARDIAC AND PULMONARY COMPLICATION PROBABILITIES AFTER BREATHING ADAPTED RADIOTHERAPY FOR BREAST CANCER

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Purpose: Substantial reductions of cardio-pulmonary radiation doses can be achieved using voluntary deep inspiration breath-hold (DIBH) or free breathing inspiration gating (IG) in radiotherapy after conserving surgery for breast cancer. The purpose of this study is to evaluate the radiobiological implications of such dosimetric benefits.

Methods and Materials: Patients from previously reported studies were pooled for a total of 33 patients. All patients underwent DIBH and free breathing (FB) scans, and 17 patients underwent an additional IG scan. Tangential conformal treatment plans covering the remaining breast, internal mammary, and periclavicular nodes were optimized for each scan, prescription dose 48 Gy. Normal tissue complication probabilities were calculated using the relative seriality model for the heart, and the model proposed by Burman *et al.* for the lung.

Results: Previous computed tomography studies showed that both voluntary DIBH and IG provided reduction of the lung V_{50} (relative volume receiving more than 50% of prescription dose) on the order of 30–40%, and a 80–90% reduction of the heart V_{50} for left-sided cancers. Corresponding pneumonitis probability of 28.1% (range, 0.7–95.6%) for FB could be reduced to 2.6% (range, 0.1–40.1%) for IG, and 4.3% (range, 0.1–59%) for DIBH. The cardiac mortality probability could be reduced from 4.8% (range, 0.1–23.4%) in FB to 0.5% (range, 0.1–2.6%) for IG and 0.1% (range, 0–3.0%) for DIBH.

Conclusions: Remarkable potential is shown for simple voluntary DIBH and free breathing IG to reduce the risk of both cardiac mortality and pneumonitis for the common technique of adjuvant tangential breast irradiation. © 2006 Elsevier Inc.

Breast cancer, Breath-hold, Gating, Radiobiology, NTCP.

INTRODUCTION

Tangential photon field breast cancer radiotherapy is mainly employed adjuvantly to breast-conserving surgery to improve local control and survival (1). For these otherwise healthy women, a primary concern is unwanted pulmonary and cardiac irradiation, which implies a risk of late injury (1, 2). This is particularly the case when the ipsilateral internal mammary nodes and periclavicular lymph nodes are included in the target definition, implying use of deep tangential fields (3, 4).

It has been demonstrated in several studies that breathing adaptation techniques can be used to reduce the irradiated heart and lung volumes, primarily by utilizing lung inflation which dilutes the amount of lung tissue in the radiation fields and spatially separates the heart from the target. An active breathing control (ABC) device has been used to "freeze" the lung volume at 75% of maximum inspiration capacity, providing significant lung and heart dose reductions (5). This approach has been proven to be clinically viable in subsequent studies (6). Recently, we have shown in two computed tomography studies that both voluntary deep inspiration breath-hold and free breathing inspiration gating can provide similar lung and heart dose reductions (7, 8). Dosimetric effects of internal margin modifications reflecting the target motion for different breathing techniques were also examined. The free breathing inspiration gating technique implemented with the RPM system (Varian Medical Systems, Inc., Palo Alto, CA) is presently in routine clinical use at our institution. The breathing adaptation techniques reported by Pedersen *et al.* (7) and Korreman *et al.* (8) furthermore maintain the target dose coverage and homogeneity, and do not compromise doses to contralateral

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organs. The aforementioned two studies provide the dosimetric data used in the present study to evaluate the radiobiological consequences of the techniques. The present study is the first to evaluate radiobiological consequences for normal tissues of the free breathing inspiration gating technique for breast cancer, and in addition, it is the first to evaluate effects of internal margin modifications on normal tissue complication probability (NTCP) magnitudes.

METHODS AND MATERIALS

A total of 33 patients referred for adjuvant radiotherapy after breast-conserving surgery for breast cancer were accrued to this study in the period March 2002 to January 2003, in accordance with a protocol approved by the Scientific Ethical Committees of Copenhagen and Frederiksberg, Copenhagen, Denmark (#KF 01-004/02). Eligibility criteria were age >50 years, radical breast-conserving surgery, and axillary lymph node metastases. Patients were included consecutively provided informed consent had been obtained. One patient was excluded from the study because of poor compliance. Of the remaining 32 patients, 15 had left-sided, 16 had right-sided, and 1 had bilateral breast cancer. For these patients, the median age was 59 (range, 45–79) years.

These patients have previously been reported as two separate groups, which are pooled for the purposes of the present study. The two groups were identical with respect to presenting diagnosis, cancer site, age, and general performance, thus justifying pooling the two groups. Previous results from each of the two groups with respect to dosimetric benefits of deep inspiration breath-hold confirmed identical heart and lung dose reductions (8).

The Varian RPM system was installed on a Siemens Somatom Plus 4 single slice scanner (Siemens AG, Munich, Germany) for respiration monitoring and automatic respiratory gating of the scanner. Each patient underwent several computed tomographic scans in different breathing phases, including a standard free breathing (FB) spiral scan, deep inspiration breath-hold (DIBH), end-expiration breath-hold, inspiration gating (IG), and free breathing expiration gating, as described in detail by Pedersen *et al.* (7) and Korreman *et al.* (8). All patients received DIBH and FB scans, and a subgroup of 17 patients underwent additional IG scans. In both previous studies, it was concluded that the use of expiration techniques resulted in an increase of doses to organs at risk, and we will therefore not address these techniques further.

Volume delineation and treatment planning were performed using the CadPlan treatment planning system (Varian Medical Systems Inc.), as described in the study of Korreman *et al.* (8). Among others, lungs, heart, clinical target volume–breast, and clinical target volume–internal mammary nodes were delineated in all scans by the same physician for consistency. A three-field mono-isocentric 6/8-MV photon technique was used, with two deep tangential fields abutting an anterior supraclavicular field half-beam. Wedges were used when appropriate for target dose homogeneity, and multileaf collimator shaping of fields was employed for conformity. Treatment plans were performed using both standard margins and margins modified according to breathing techniques. Modified clinical target volume to planning target volume margins were determined for each breathing technique, based on a patient population mean of the recorded chest wall excursion during beam-on time. During DIBH, the chest wall excursion was slightly larger than during FB, implying an increased modified margin. For IG, a duty cycle of approximately 25% of the entire breathing cycle was chosen, leading to a slightly decreased modified margin compared with FB.

All plans were individually optimized by the same physicist for consistency. The prescription dose was 48 Gy in 24 fractions.

Radiobiological modeling of NTCP magnitudes will be performed using well-established models from the literature. Probability for cardiac mortality was calculated using the relative seriality model proposed by Gagliardi *et al.* (9) for the entire heart volume. Within this model, the cardiac mortality complication probability can be calculated as

$$NTCP_{heart} = \left\{1 - \prod_{i=1}^{n} \left[1 - P(D_i)^s\right]^{\triangle v_i}\right\}^{1/s}$$

$$P(D_i) = 2^{-\exp\{e\gamma(1 - D_i/D_{50})\}} \qquad (1)$$

The relative seriality factor (s) used was 1, and the maximum relative slope of the dose–response curve (γ) was 1.28. The dose resulting in a 50% complication probability for the heart, D_{50}, was 52.3 Gy. The parameter magnitudes were found in the study by Gagliardi *et al.* (9) by fitting the model to clinical incidence of cardiac mortality for groups of breast cancer patients from two randomized trials.

For pneumonitis probability, the model proposed by Burman *et al.* (10) and adapted to nonuniform doses by dose–volume histogram reduction (11) was used. Within this model, the complication probability for pneumonitis can be calculated as

$$NTCP_{lung} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{u^2}{2}\right) du$$

$$t = \frac{(D_{eff} - D_{50})}{mD_{50}}, \quad D_{eff} = \left(\sum_i D_i^{1/n} \frac{V_i}{V_{tot}}\right)^n \qquad (2)$$

The parameter describing the volume dependence (n) is 0.87, and the slope of complication probability vs. dose (m) is 0.18. D_{50} is 24.5 Gy. These parameter magnitudes are as proposed by Burman *et al.* (10), and are based on fitting of the model to data from the work of Emami *et al.* (12).

For each patient and for each breathing technique, NTCP values were calculated as stated above with and without modified margins. Paired Wilcoxon tests were used to estimate statistical significance of the differences between NTCP values for different breathing techniques and internal margins.

RESULTS

The dose distributions obtained by Pedersen *et al.* (7) and Korreman *et al.* (8) constitute the basis for the calculations in this study, and are illustrated in Figs. 1 and 2. In Fig. 1, examples of heart and ipsilateral lung dose–volume histograms are shown for a representative patient with left-sided cancer, using results from plans with modified internal breathing margins. The two expiration techniques performed worse than the standard FB technique, and are therefore not discussed further in this study. Both inspiration techniques performed better than the FB standard, and not much differently from each other especially with respect to heart dose. An important result of Korreman *et al.* (8) was in fact that DIBH and IG with modified margins were very

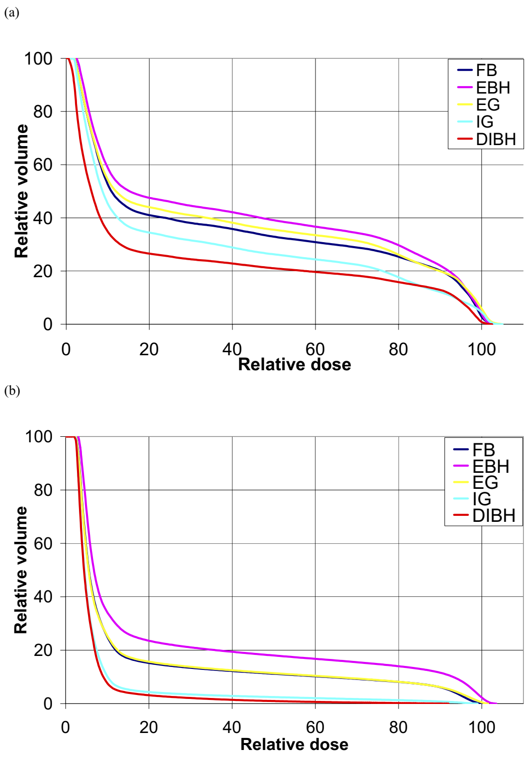

Fig. 1. Example dose–volume histograms for (a) ipsilateral lung and (b) whole heart comparing the free-breathing (FB; blue), end-expiration breath-hold (EBH; magenta), end-expiration gating (EG; yellow), end-inspiration gating (IG; cyan), and deep inspiration breath-hold (DIBH; red) plans for the same patient with left-sided cancer.

similar in terms of dose–volume histograms. This is illustrated in Fig. 2 showing a graphical representation of the distributions of lung and heart V_{50} (relative volumes receiving more than 50% of the prescription dose) for DIBH, IG, and FB with and without modified margins, for the population of patients in (8).

In Tables 1 and 2, the heart and lung NTCP values are given for all patients for DIBH, IG, and FB with and without modified margins.

For the FB technique, 5 of 33 patients (15.2%) had a lung pneumonitis NTCP below 5%. For DIBH, this was increased to 19 of 32 (59.4%), and for IG to 10 of 16 (62.5%). The median pneumonitis NTCP was 4.3% (range, 0.1–59%) for DIBH (with modified margin), 2.6% (range, 0.1–40.1%) for IG (with modified margin), and 28.1% (range, 0.7–95.6%) for FB. The difference between DIBH and IG is not statistically significant ($p > 0.3$), whereas the differences between both inspiration techniques and FB are significant ($p \leq 0.0002$).

With respect to cardiac mortality, 3 of 16 patients (18.8%) had a NTCP below 1% in FB, whereas in IG this ratio was increased to 6 of 9 patients (66.7%). For DIBH, 13 of 16 patients (81.3%) had a NTCP below 1%—and as many as 50% of the patients had a NTCP of 1‰ or below.

The median cardiac mortality NTCP was 0.1% (range, 0–3.0%) for DIBH, 0.5% (range, 0.1–2.6%) for IG (both inspiration techniques with modified margins), and 4.8% (range, 0.1–23.4%) for FB. Again, the difference between DIBH and IG is not statistically significant ($p > 0.1$), whereas the differences between both inspiration techniques and FB are significant ($p < 0.005$). In Fig. 3, the distributions of NTCP values for pneumonitis and cardiac mortality over the population of patients are illustrated using the same graphical representation as in Fig. 2.

The differences between plans with and without modified margins were small but statistically significant ($p \leq 0.005$). The differences between median NTCP values were between 0 and 2.5% points, and were thus much smaller than the differences between inspiration and FB techniques. Introducing inspiration techniques therefore has a substantial effect regardless of whether margins are modified.

DISCUSSION

This computed tomographic study shows remarkable reductions in NTCP values for both pneumonitis and cardiac mortality for adjuvant breast cancer radiotherapy with two

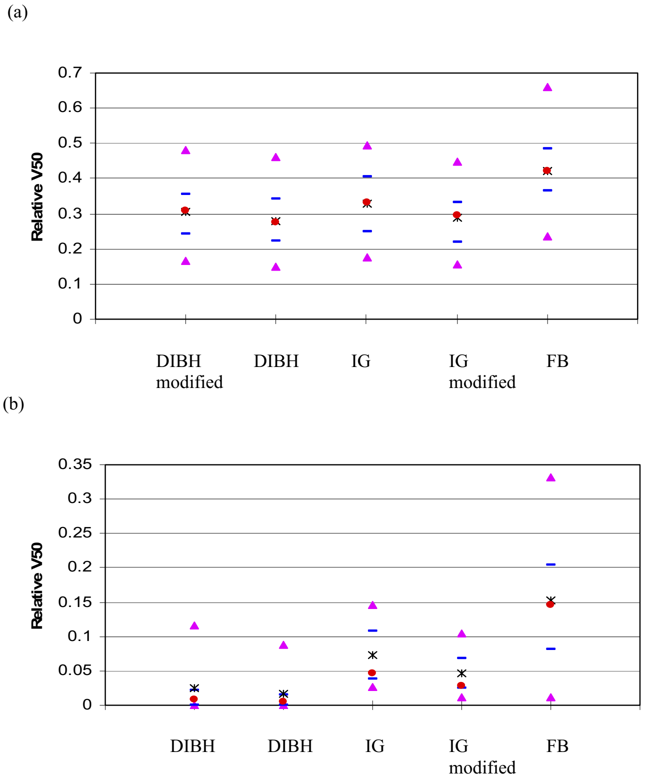

Fig. 2. The distribution of relative V_{50} (relative volume receiving more than 50% of prescription dose) over the population of patients for (a) ipsilateral lung and (b) whole heart (only patients with left-sided cancers). The magenta triangles (▲) indicate maximum and minimum V_{50}, the blue horizontal lines (-) indicate the 25% and 75% fractiles, the star (*) indicates mean and the red dot (●) median values. The distributions are shown for deep inspiration breath-hold (DIBH) with modified margin, deep inspiration breath-hold with standard margin, inspiration gating (IG) with modified margin, inspiration gating with standard margin, and free breathing (FB) (standard margin).

Table 1. NTCP for pneumonitis for all patients in DIBH, IG, and FB with and without modified margins (given as percent numbers)

Patient number	DIBH modified margin	DIBH standard margin	IG modified margin	IG standard margin	FB
1	1.4	1.1	—	—	14.7
2	15.7	13.2	—	—	28.1
3	59.0	47.0	—	—	73.7
4	6.2	3.4	—	—	9.6
5	0.2	0.1	—	—	2.1
6	4.2	1.6	—	—	26.9
7 sin	3.3	2.0	—	—	11.1
7 dex	11.7	9.2	—	—	46.5
8	34.8	17.9	—	—	50.8
9	0.3	0.3	—	—	16.3
10	4.2	2.3	—	—	51.8
11	11.7	2.4	—	—	23.4
12	4.4	3.7	—	—	10.5
13	4.9	3.0	—	—	11.2
14	20.6	9.5	—	—	68.0
15	0.1	0.1	—	—	3.0
16	29.4	18.9	16.0	32.6	61.7
17	1.6	0.5	2.5	5.1	48.4
18	0.4	0.3	2.0	2.2	9.1
19	0.1	0.02	0.2	0.4	1.4
20	0.1	0.05	0.4	0.7	30.4
21	20.1	12.9	4.3	16.4	31.0
22	0.7	0.4	1.3	2.8	14.8
23	10.1	5.6	10.0	19.9	58.0
24	37.1	28.2	40.1	58.0	95.6
25	1.2	0.3	2.6	6.1	31.6
26	0.1	0.02	0.1	0.4	55.1
27	4.7	2.6	6.2	13.2	41.8
28	7.9	4.6	8.1	28.9	62.4
29	0.6	0.3	0.2	0.9	2.2
30	3.4	0.9	—	—	23.8
31	—	—	0.1	0.1	0.7
32	12.6	10.1	7.0	21.7	75.7
Median	4.3	2.4	2.6	5.1	28.1

Abbreviations: DIBH = deep inspiration breath-hold; FB = free breathing; IG = inspiration gating; NTCP = normal tissue complication probability; dex = right; sin = left.

inspiration breathing adaptation techniques, namely voluntary DIBH and free breathing IG, as compared with FB. No significant differences were found between NTCP values for the two different inspiration techniques. Qualitatively, these results closely reflect the cardio-pulmonary dosimetric improvements with inspiration techniques reported in Pedersen *et al.* (7) and Korreman *et al.* (8) for the same patient population. Because the dose–volume histograms are generally lower for inspiration techniques than for FB, this is expected to be the case. Quantitatively, the reductions in NTCP values are not only significant, they are also very large for both heart and lung, emphasizing the striking benefits that can be achieved with breathing adaptation techniques for breast cancer radiotherapy. The benefits are most remarkable with respect to cardiac mortality NTCP values, for which the median of the relative reductions from FB to DIBH (modified margin) was 97% ((NTCP(FB)-NTCP(DIBH))/NTCP(FB)). This magnitude reflects the pronounced dosimetric benefits, with a corresponding relative reduction in V_{50} of 91%. It is noteworthy that a substantial amount of the heart dose reduction anatomically takes place in the anterior part of the heart where the left coronary artery is present. In Pedersen *et al.* (7) and Korreman *et al.* (8) we observed even larger reductions in irradiated coronary artery volumes (median of relative reductions from FB to DIBH of 96%) than whole heart reductions. The actual reduction in risk of ischemic disease may therefore be larger than that suggested by the calculated NTCP values for the whole heart.

For pneumonitis NTCP, the median of the relative reductions from FB to DIBH (modified margin) was 84%, whereas the corresponding reduction in V_{50} was only 30%. The large magnitude of the reduction in NTCP is the result of large relative variations in the dose variable t with corresponding variations in the dose volume reduction parameter D_{eff}, when the slope parameter m is small, and D_{eff} is in the vicinity of D_{50} as is the case for the lung dose–volume histograms in this study.

In this context, it is important to be aware of the limitations in the dose calculation algorithms used for the computation of dose distributions used for the present study. As described in Pedersen *et al.* (7) and Korreman *et al.* (8), all dose calculations for this study were performed using a pencil-beam algorithm. In the pencil-beam approximation, lateral electron transport is not adequately accounted for in low-density tissue such as lung, and the dose distribution calculated with the pencil-beam algorithm gives dose distributions for lung with a gradient across the 50% isodose border appearing larger than it really is. The smaller the

Table 2. NTCP for cardiac mortality for all patients with left-sided cancer in DIBH, IG, and FB with and without modified margins (given as percent numbers)

Patient number	DIBH modified margin	DIBH standard margin	IG modified margin	IG standard margin	FB
1	0	0	—	—	0.5
2	0.3	0.2	—	—	2.7
3	3.0	2.1	—	—	5.8
4	0.04	0	—	—	0.1
5	0.1	0	—	—	1.7
6	0	0	—	—	0.1
7 sin	0	0	—	—	1.7
16	1.7	0.9	1.3	3.0	9.0
17	0.3	0.1	0.4	0.8	5.4
18	0.1	0.1	0.5	0.5	3.2
19	0	0	0.1	0.5	23.4
20	0	0	0.3	0.4	5.1
21	1.7	1.2	0.7	2.0	4.5
22	0	0	0.3	0.7	6.4
23	0.2	0.1	1.9	2.6	6.1
24	0.2	0.2	2.6	3.9	10.7
Median	0.1	0.1	0.5	0.8	4.8

Abbreviations: DIBH = deep inspiration breath-hold; FB = free breathing; IG = inspiration gating; NTCP = normal tissue complication probability; sin = left.

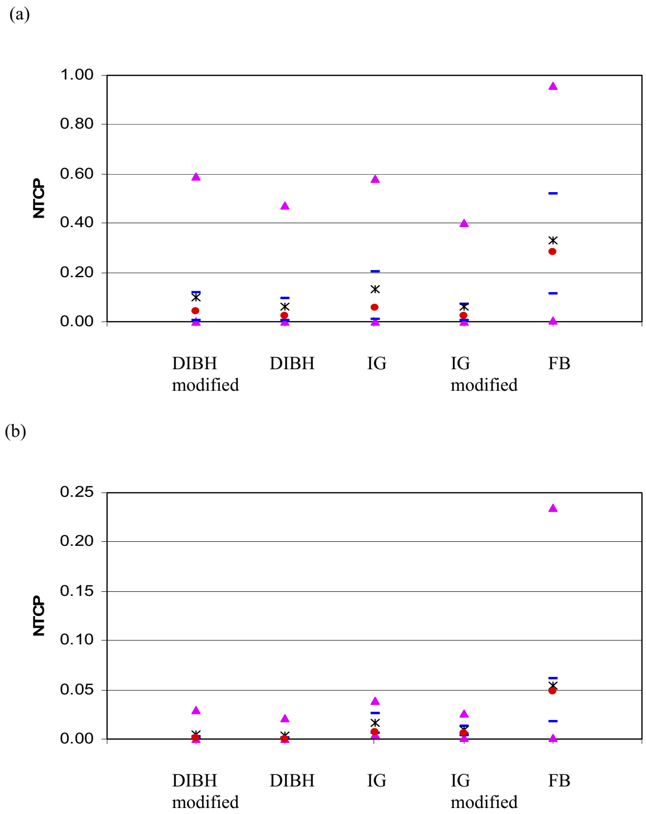

Fig. 3. The distribution of normal tissue complication probability values over the population of patients for (a) pneumonitis of ipsilateral lung and (b) cardiac mortality (only patients with left-sided cancers). The magenta triangles (▲) indicate maximum and minimum V_{50} (relative volume receiving more than 50% of prescription dose), the blue horizontal lines (-) indicate the 25% and 75% fractiles, the star (*) indicates mean and the red dot (●) median values. The distributions are shown for deep inspiration breath-hold (DIBH) with modified margin, deep inspiration breath-hold with standard margin, inspiration gating (IG) with modified margin, inspiration gating with standard margin, and free breathing (FB) (standard margin).

density in the lung tissue, the smaller the actual dose gradient, and the more incorrect is the pencil-beam approximation. This effect is reflected over the entire dose range in the dose–volume histograms of the treatment plans, and thus affects the NTCP calculations. With respect to lung, a more accurate dose calculation will result in dose–volume histograms with a larger slope than that seen for pencil-beam calculations; an effect increasing with increasing lung inflation. Examples of dose–volume histograms illustrating this for lung with low density (DIBH) calculated with the pencil-beam algorithm and with the three-dimensional convolution collapsed cone (CCC) algorithm (Helax TMS was used for both calculations) are shown in Fig. 4. The collapsed cone convolution algorithm has been shown to give more correct dose distributions in lung than the pencil-beam approach (13, 14).

In the example illustrated in Fig. 4, the NTCP values (pneumonitis) calculated with the CC algorithm would be 30.1% for DIBH and 51.7% for end-expiration gating, whereas the NTCP values calculated with the pencil-beam algorithm are 46.9% and 66.4% (end-expiration gating). The NTCP values for CC are lower than those for the pencil beam, because the high-dose ends of the histograms contribute with a larger weight (since the dose is weighted to the power $1/n$) to the D_{eff}'s than the low-dose ends, and the high-dose ends generally have larger magnitudes with the pencil beam than with the CC algorithms.

With respect to calculations for cardiac mortality, the picture is less clear than for pneumonitis calculations. In general, the whole heart dose–volume histograms are slightly translated toward lower doses when the more correct CC algorithm is used than when the pencil-beam algorithm is used. The shift expectedly should give rise to lower NTCP values with the CC algorithm than with the pencil-beam algorithm—again an effect that should be more pronounced the lower the lung density.

Thus, the results of this study in favor of the inspiration techniques—in terms of pneumonitis NTCP values—can be expected to be enhanced if more correct dose calculation algorithms were used. With respect to cardiac mortality, the relative differences between breathing phases is more or less conservative to dose calculation algorithm.

However, applying clinical outcome models to dose–volume histograms resulting from dose calculation algorithms of increasing sophistication is not a trivial matter. The models are generally based on historic outcome data related to doses calculated with primitive algorithms—refining the dose calculation algorithms naturally does not change the statistical incidence of complications. Therefore, changes in dose calculation algorithms should be accompanied by corresponding parameter changes in the clinical outcome models. This causal relation warrants the use of the pencil-beam dose calculation algorithm in conjunction with the clinical outcome models and model parameters in the present study.

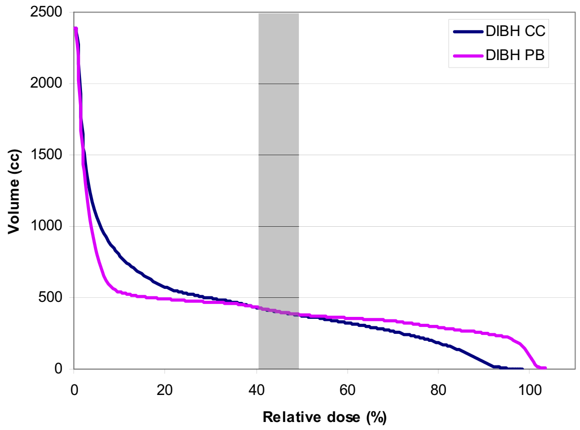

Fig. 4. Dose–volume histograms for ipsilateral lung in deep inspiration breath-hold (DIBH) calculated with the pencil-beam (PB) (magenta) and with the three-dimensional convolution collapsed cone (CC) (blue) algorithms. The hatched area indicates the dose region where the calculated volumes are more or less conservative to calculation algorithm.

In the study of Remouchamps *et al.* (5), several different breast irradiation techniques were compared including deep tangents with intensity-modulated radiation therapy (missing tissue compensation) during FB and moderate DIBH using an active breathing control device. NTCP values for cardiac mortality and pneumonitis were calculated using the same models as those used in the present study. The prescription dose level was 50 Gy in the study of Remouchamps *et al.* (5) (compared with 48 Gy in this study), and the fractionation scheme was different using fractions of 1.8 Gy. Using the linear-quadratic model to convert this to the equivalent dose at 2 Gy fractions, values of 48.4 Gy for the heart [$\alpha/\beta \approx 3$ Gy (9)] and 48.5 Gy for the lung [$\alpha/\beta \approx 3.3$ Gy (15)] are found, which are both close to the 48 Gy total dose in this study. We can therefore compare NTCP numbers between the studies. The treatment techniques in the two studies are also similar except that in the present study wedges were used for target dose homogenization. The NTCP values obtained during FB are similar for the two studies, but the improvements with DIBH (unmodified margins) are substantially larger in this study than in the study of Remouchamps *et al.* (5), especially for lung. The relative reduction in mean lung NTCP was 66% in Remouchamps *et al.* (5) compared with 81% in this study. For heart NTCP, the relative reduction was 85% in the study of Remouchamps *et al.* (5) compared with 94% in this study. The difference is possibly due to the fact that in the work by Remouchamps *et al.* (5), a moderate deep inspiration breath-hold was used (75% of maximum inspiration capacity), whereas in this study patients were asked to hold their breath at a comfortable maximum level.

CONCLUSION

This study demonstrates the potential for voluntary DIBH and free breathing IG to reduce the risk of cardiac mortality and pneumonitis for the common technique of adjuvant irradiation after conservative surgery for breast cancer. With respect to pneumonitis, the relative reduction is on the order of 85%, and for cardiac mortality the reduction is as large as approximately 95%.

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