Table 1. V95, V90 and D98 of the planning target volume for evaluation (PTV_EV) on field-in-field (FIF) techniques for each patient

Patient #	Monitor unit (a)	V95 (%)			V90 (%)			D98 (Gy)		
		FIF_0	FIF_5	FIF_10	FIF_0	FIF_5	FIF_10	FIF_0	FIF_5	FIF_10
R-1	237 (14)	92.2	*90.3*	*90.6*	99.3	99.3	99.9	45.8	45.8	46.0
R-2	231 (11)	93.4	96.2	95.5	100.0	100.0	100.0	46.9	47.2	47.1
R-3	234 (12)	99.5	99.6	99.6	100.0	100.0	100.0	48.3	48.4	48.4
R-4	238 (12)	99.3	99.3	99.3	100.0	100.0	100.0	48.2	48.2	48.2
R-5	233 (16)	96.4	*96.2*	*93.4*	100.0	100.0	100.0	47.3	47.3	*47.0*
R-6	227 (14)	83.2	*82.3*	*77.5*	95.4	*95.3*	*92.5*	44.1	*44.0*	*43.8*
R-7	237 (15)	98.3	*98.2*	*97.8*	100.0	100.0	100.0	47.6	47.6	*47.5*
R-8	228 (12)	91.8	*91.6*	*89.2*	99.0	99.0	99.0	45.6	45.6	*45.5*
R-9	240 (13)	88.6	*88.4*	*86.1*	98.3	98.3	*98.2*	45.2	45.2	45.2
R-10	237 (12)	95.4	95.4	*94.3*	99.9	99.9	99.9	46.6	46.6	*46.4*
L-1	232 (12)	92.1	92.2	88.0	99.9	99.9	99.9	46.0	46.2	46.0
L-2	239 (12)	72.2	*71.3*	*66.7*	94.9	*94.8*	*94.4*	44.1	44.1	*44.0*
L-3	250 (15)	87.9	87.9	*87.7*	100.0	100.0	100.0	46.2	46.2	46.2
L-4	232 (10)	99.5	99.5	99.5	100.0	100.0	100.0	48.3	48.3	48.3
L-5	240 (18)	87.0	*86.1*	*82.7*	98.3	98.3	*97.8*	45.2	45.2	*45.0*
L-6	235 (14)	89.4	*87.3*	*85.9*	99.4	*99.3*	*96.3*	45.7	*45.6*	*44.8*
L-7	238 (12)	94.9	94.9	94.9	99.9	99.9	99.9	46.8	46.9	47.0
L-8	238 (12)	97.3	97.3	97.3	99.9	99.9	99.9	47.4	47.4	*47.3*
L-9	243 (15)	92.0	*91.8*	*90.9*	99.0	99.0	99.0	45.6	45.6	45.6
L-10	232 (10)	97.4	97.5	97.4	100.0	100.0	100.0	47.4	47.5	47.4
Average	232 (13)	92.4	*92.2*	*90.7*	99.2	*99.1*	*98.8*	46.4	46.4	*46.3*

V95 (90) is the percentage of the PTV_EV that receives more than 95% (90%) of the prescribed dose; D98 is the dose received by 98% of the PTV_EV; FIF_0, FIF_5 and FIF_10 are the virtual plans for FIF techniques with moving isocenters to the posterior direction with 0 (original plan), 5 and 10 mm, respectively; numbers are shown in italics when the values are smaller than those on FIF_0.
[a]Monitor unit of the reduction fields.

virtual plans using a physical wedge with a 15° angle were made and the same measurements were taken on the same 20 patients (Wedge_5 and Wedge_10).

The calculation algorithm was CC Convolution. The grid size of the calculation matrix was 2 mm.

We used GraphPad Prism version 5 (GraphPad Software Inc.) for statistical analysis. The paired *t*-test was used to compare the results for FIF and wedge techniques. Differences were deemed significant when two-tailed *P* values were <0.05.

RESULTS

The mean total MU was 236 (range: 227–250) per 2 Gy. The mean percentage of MU of the reduction fields was 5.5% (4.3–7.5). The mean V90, V95 and D98 of the PTV_EV on FIF techniques were 99.2% (94.9–100), 92.4% (72.2–99.5) and 46.4 Gy (44.1–48.3), respectively, whereas the mean V90, V95 and D98 on wedge plans were 99.8% (97.9–100), 96.5% (82.8–100) and 47.4 Gy (45.0–49.0), respectively (Tables 1 and 2). The differences in D98 between the original plans and virtual scenarios for FIF techniques were significantly smaller than those for wedge techniques (Table 3). No statistically significant differences were observed in the differences in V90 and V95 between plans for FIF techniques and those for wedge techniques (Table 3).

DISCUSSION

To the best of our knowledge, this is the first report to focus on the dosimetric impact of geometrical uncertainties in FIF techniques for whole breast radiotherapy. Several groups have reported that geometrical uncertainties have a considerable impact on intensity-modulated radiation therapy (IMRT) dose distributions (8–11). Although the FIF technique is a kind of

Table 2. V95, V90 and D98 of the PTV_EV on wedge plans for each patient

Patient #	Monitor unit	V95 (%)			V90 (%)			D98 (Gy)		
		W_0	W_5	W_10	W_0	W_5	W_10	W_0	W_5	W_10
R-1	322	96.1	96.4	96.1	99.9	100.0	100.0	46.6	46.8	46.8
R-2	316	97.4	*96.7*	*95.2*	100.0	100.0	100.0	47.4	*47.3*	*47.1*
R-3	318	100.0	*99.9*	*99.8*	100.0	100.0	100.0	49.0	*48.8*	*48.4*
R-4	323	99.9	99.9	99.9	100.0	100.0	100.0	49.0	*48.8*	*48.6*
R-5	317	99.4	*98.8*	*97.5*	100.0	100.0	100.0	48.0	*47.7*	*47.5*
R-6	310	88.1	*85.8*	*82.6*	97.9	*97.4*	*96.7*	45.0	*44.9*	*44.6*
R-7	322	99.7	99.7	*99.6*	100.0	100.0	100.0	48.5	*48.3*	*48.1*
R-8	293	96.2	*95.7*	*95.0*	100.0	100.0	100.0	46.9	*46.8*	*46.6*
R-9	326	94.8	*94.0*	*92.5*	99.6	*99.5*	*99.4*	46.3	*46.2*	*46.0*
R-10	323	98.4	*98.1*	*97.6*	100.0	100.0	100.0	47.7	*47.6*	*47.4*
L-1	316	99.1	*98.3*	*96.8*	100.0	100.0	100.0	47.9	*47.6*	*47.3*
L-2	325	82.8	*82.0*	*80.1*	98.3	*97.9*	*97.3*	45.1	*45.0*	*44.8*
L-3	340	97.3	97.7	97.6	100.0	100.0	100.0	47.4	47.5	47.5
L-4	317	99.9	99.9	*99.7*	100.0	100.0	100.0	48.9	*48.7*	*48.4*
L-5	324	92.7	*91.7*	*90.1*	99.8	*99.7*	*99.6*	46.4	*46.2*	*46.0*
L-6	321	96.3	*95.1*	*92.8*	100.0	100.0	100.0	47.2	*47.0*	*46.7*
L-7	324	99.1	*98.7*	*98.1*	100.0	100.0	100.0	47.9	*47.7*	*47.6*
L-8	322	99.2	*99.0*	*98.5*	100.0	100.0	100.0	48.1	*47.9*	*47.7*
L-9	328	95.4	*94.5*	*93.2*	100.0	100.0	100.0	46.7	*46.5*	*46.3*
L-10	314	97.4	*97.2*	*96.6*	100.0	100.0	100.0	47.4	47.4	47.4
Average	320	96.5	*96.0*	*95.0*	99.8	99.7	99.7	47.4	*47.2*	*47.0*

V95 (90) is the percentage of the PTV_EV that receives more than 95% (90%) of the prescribed dose; D98 is the dose received by 98% of the PTV_EV; Wedge_0, Wedge_5 and Wedge_10 are the virtual plans for a physical wedge, moving isocenters to the posterior direction by 0, 5 and 10 mm, respectively; numbers are shown in italics when the values are smaller than those on Wedge_0.

Table 3. The mean differences (range) of V95, V90 and D98 between original plans and virtual scenarios

	V95	V90	D98
FIF_5	−0.2% (−2.1 to +2.8)	−0.02% (−0.1 to 0)	0 Gy (−0.1 to +0.3)
Wedge_5	−0.5% (−2.3 to +0.4)	−0.05% (−0.5 to +0.1)	−0.2 Gy (−0.3 to 0.2)
P	0.28	0.3	**<0.01**
FIF_10	−1.7% (−5.7 to +2.1)	−0.3% (−3.1 to +0.6)	−0.1 Gy (−0.9 to +0.2)
Wedge_10	−1.5% (−5.5 to +0.3)	−0.1% (−1.2 to +0.1)	−0.4 Gy (−0.6 to 0.2)
P	0.76	0.38	**<0.01**

V95 (90) is the percentage of the volume of the PTV_EV which receives more than 95% (90%) of the prescribed dose; D98 is the dose that 98% of the PTV_EV receives; FIF_5 (FIF_10) is the virtual plan for FIF techniques with moving isocenters to the posterior direction with 5 (10 mm); Wedge_5 (Wedge_10) is the virtual plan for a physical wedge, moving isocenters to the posterior direction by 5 (10 mm). The bold values indicate statistically significant differences.

IMRT, our results showed that the quantity of the cold spots caused by geometrical uncertainties in FIF techniques for whole breast radiotherapy was similar to that in wedge plans. This might be partly because the proportion of the reduction fields was quite low. Most patients do not need a high MU for reduction fields, but caution might be needed when the proportion of the reduction fields is a little larger.

Several groups have reported that the FIF technique can reduce dose inhomogeneity in whole breast radiotherapy compared with that using physical wedge techniques (3–7).

An additional benefit of using the FIF technique is that FIF techniques can reduce MU and dose in the contralateral breast. Lee et al. (3) have reported that the volumes in the contralateral breast that receive more than 2 Gy with a prescription dose of 50.4 Gy were 0.3% for FIF techniques, but 2.0% for physical wedge techniques ($P < 0.01$). By using the FIF techniques, the incidence of radiation-induced contralateral breast cancer might be reduced.

The possible disadvantage of using the FIF techniques is that FIF techniques may increase the uncertainties of dose calculation on the TPS. If we use fields that are too small or too irregular as the reduction fields, the TPS may not calculate the MU and the dose distributions accurately. Furthermore, if we prescribe MU that is too small, the output from the linear accelerator may become unstable. In such cases, dosimetric verification should be done for each plan. For this reason, we regulate the in-house protocol as described in the Patients and Methods section to ensure the accuracy of the TPS when we use FIF techniques in order to eliminate the necessity of dosimetric verification for individual plans.

A limitation of this study is that it evaluated a small series of patients and does not have sufficient statistical power to recognize potential differences in V90 and V95 between plans for FIF techniques and those for wedge techniques. Nevertheless, the outcomes of this study offer some guidance to clinicians in an area where data are lacking and show that the quantity of cold spots caused by geometrical uncertainties in FIF techniques is similar to that using wedge techniques.

In conclusion, the quantity of cold spots caused by geometrical uncertainties in FIF techniques for whole breast radiotherapy was similar to that on for the wedge techniques and was acceptable.

Conflict of interest statement

None declared.

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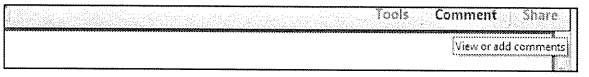

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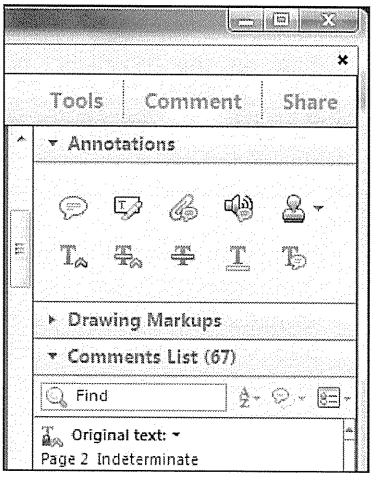

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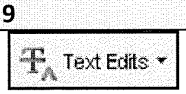
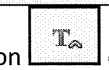
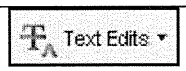
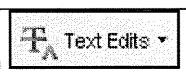
Insert text	Click the 'Text Edits' button  on the Commenting tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on 'x' in the top right-hand corner.	Click the 'Insert Text' icon  on the Comment tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on '_'  in the top right-hand corner.
Replace text	Click the 'Text Edits' button  on the Commenting tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).	Click the 'Replace (Ins)' icon  on the Comment tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).
Remove text	Click the 'Text Edits' button  on the Commenting tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.	Click the 'Strikethrough (Del)' icon  on the Comment tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.
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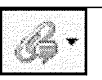
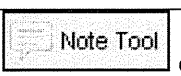
Attach a file	Click on the 'Attach a File' button  on the Commenting tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. To make a comment, go to 'General' in the 'Properties' window, and then 'Description'. A graphic will appear in the PDF file indicating the insertion of a file.	Click on the 'Attach File' icon  on the Comment tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. A graphic will appear indicating the insertion of a file.
Leave a note/ comment	Click on the 'Note Tool' button  on the Commenting tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.	Click on the 'Add Sticky Note' icon  on the Comment tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.

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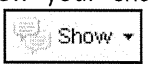
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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Clinical Investigation

Identifying Patients Who Are Unsuitable for Accelerated Partial Breast Irradiation Using Three-dimensional External Beam Conformal Techniques

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Summary

Fifty consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) accelerated partial breast irradiation (APBI) techniques. Dose–volume histogram (DVH) constraints were satisfied in 20% of patients with a long craniocaudal surgical clip distance (CCD; ≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Patients with long CCDs might be unsuitable for 3D-CRT APBI due to nonoptimal DVH constraints.

Purpose: Several recent studies reported that severe late toxicities including soft-tissue fibrosis and fat necrosis are present in patients treated with accelerated partial breast irradiation (APBI) and that these toxicities are associated with the large volume of tissue targeted by high-dose irradiation. The present study was performed to clarify which patients are unsuitable for APBI to avoid late severe toxicities.

Methods and Materials: Study subjects comprised 50 consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery, and in whom five or six surgical clips were placed during surgery. All patients were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) APBI techniques according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 and Radiation Therapy Oncology Group (RTOG) 0413 protocol. The beam arrangements included mainly noncoplanar four- or five-field beams using 6-MV photons alone.

Results: Dose–volume histogram (DVH) constraints for normal tissues according to the NSABP/RTOG protocol were satisfied in 39 patients (78%). Multivariate analysis revealed that only long craniocaudal clip distance (CCD) was correlated with nonoptimal DVH constraints ($p = 0.02$), but that pathological T stage, anteroposterior clip distance (APD), site of ipsilateral breast (IB) (right/left), location of the tumor (medial/lateral), and IB reference volume were not. DVH constraints were satisfied in 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Median IB reference volume receiving ≥50% of the prescribed dose (IB-V_{50}) of all patients was 49.0% (range, 31.4–68.6). Multivariate analysis revealed that only a long CCD was correlated with large IB-V_{50} ($p < 0.0001$), but other factors were not.

Conclusion: Patients with long CCDs (≥5.5 cm) might be unsuitable for 3D-CRT APBI because of nonoptimal DVH constraints and large IB-V_{50}. © 2012 Elsevier Inc.

Keywords: Partial breast irradiation, Breast cancer, Radiotherapy, 3D-conformal radiotherapy, Toxicity

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Introduction

Breast-conserving therapy including partial resection and postoperative whole breast irradiation has constituted standard care for patients with early breast cancer (1). Some Phase III trials of postoperative radiotherapy and systematic reviews have revealed that omission of postoperative radiotherapy increases recurrence in breasts by threefold, and increases absolute breast cancer mortality by more than 5% (1, 2). Several reasons, including the long-term radiation schedule, level of surgeon involvement in the radiation decision, patient refusal, and comorbidity, lead to omission of postoperative radiotherapy. In fact, approximately 25% of patients who underwent conservative surgery did not receive postoperative radiotherapy in the United States (1991–2002) (3).

Approximately 85% of breast recurrences after breast conservative therapy develop in the vicinity of the tumor bed; several percent appear "elsewhere" in the breast, and the absolute number of such failures is very low (4). In the past decade, prospective clinical trials and retrospective studies evaluated the efficacy and safety of accelerated partial breast irradiation (APBI) using small radiation fields and a large fraction size. These studies reported good treatment outcome and minimal late toxicities after a short follow-up duration (4–6). However, two recent studies reported that the large volume of irradiated breast tissue was correlated with higher incidences of late severe toxicities including soft-tissue fibrosis and fat necrosis of the breast, which were clearly associated with marked cosmetic compromise (7, 8). Appropriate eligibility criteria and treatment schedules for APBI should be established to avoid late severe toxicities. The present study aimed to identify patients who are unsuitable for APBI because of the potential risk of late toxicities including soft-tissue fibrosis and fat necrosis after APBI using three-dimensional conformal radiotherapy (3D-CRT).

Methods and Materials

Patients

The study population consisted of 50 consecutive patients with unilateral breast cancer, at Union for International Cancer Control 7th Stage 0–II, who received breast-conserving therapy between April 2009 and September 2009. Median patient age was 49 years (range, 33–73). The right-to-left ratio of the ipsilateral breast (IB) was 25:25, and the medial-to-lateral ratio of the tumor location was 19:31. All patients underwent partial breast resection, and five or six surgical clips were placed at the borders of the surgical bed. Thirty-one patients had pathological T stage 1 (pT1), 7 patients had pT2, and 12 patients had pTis. Sentinel node biopsy and/or axillary node dissection revealed that 47 patients had pathological N stage 0 (pN0), and 2 patients had pN1. pN stage was not evaluated for 1 patient.

Radiation treatment planning

All patients were placed in the supine position and underwent computed tomography (CT) as part of the standard planning for whole breast irradiation. CT scanning was performed using a 2-mm thick-slice and a slice step of 2 mm; slices extended to completely cover the bilateral whole breast, lung, heart, thyroid, and a 5-cm margin in the cranial and caudal directions. No respiratory control was used. The following structures were contoured for the planning of 3D-CRT: surgical clips, clinical target volume (CTV), planning target volume (PTV), ipsilateral whole breast (IB) reference, IB reference excluding PTV (IB-PTV), contralateral breast, heart, bilateral lungs, and thyroid. To keep the probability of comparison consistent with outcomes of other studies, the contouring of IB reference was made up using an automated contouring method applied by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-39) and Radiation Therapy Oncology Group (RTOG 0413) protocol (9). CTV was defined as the volume bound by uniform expansion of surgical clips by 1.5 cm in all dimensions, excluding the pectoralis muscles, chest wall, lung, heart, pericardial fat, and 5 mm beneath the skin (9). PTV was defined as the volume bound by uniform expansion of CTV by 1.0 cm in all dimensions. PTV_EVAL, the volume for dose–volume histogram (DVH) analysis, was defined as the volume of PTV excluding the first 5 mm of tissue under the skin, the posterior breast tissue extent (chest wall and pectoral muscles), lung, heart, and pericardial fat.

All 50 patients were replanned using 3D-CRT planning system software (Pinnacle^3 version 8.0m, Pinnacle Treatment System; Philips, Milpitas, CA). To correctly evaluate heterogeneous tissue density, the convolution algorithm was used. The NSABP B-39/RTOG 0413 protocol dose limitation was used as a guideline for specified normal tissue constraints (9). Beam arrangements included noncoplanar mainly four- or five-field beams using 6-MV photons referring to the method reported by Vicini *et al.* (10). No electron beam was used. The exertion of simulation planning was for minimizing doses to organs at risk, and improving a homogeneous dose to the target volume. Beam weights, beam angle, and wedge angles were manually optimized, such that the targeted goal was to cover $\geq$90% of the PTV_EVAL by a dose $\geq$90% of the prescribed dose (9). The DVH constraints adopted for plan optimization are shown in Table 1.

A total dose of 30 Gy in five fractions was prescribed to the International Commission on Radiation Units and Measurements 50 reference point dose (isocenter) (11). The isocenter was placed in the center of the PTV. This treatment schedule was proposed by the Department of Radiation Oncology at New York University using the prone position and parallel-opposed minitangents external beam therapy (12). The New York University study demonstrated that this abbreviated regimen was well tolerated, with only mild acute adverse events and excellent or good cosmetic outcome. However, given the typical Japanese woman's breast size and shape, we had patients assume a supine position and used a noncoplanar three-, four-, five-, and six-beam technique.

Data analysis

IB volume, target volumes, and distance of surgical clips were measured by CT images on the radiation treatment planning (RTP) system. The craniocaudal surgical clip distance (CCD) was defined as the longitudinal distance along the body axis between head-side clip and foot-side clip, and the anteroposterior surgical clip distance (APD) was defined as the vertical distance between anterior-side clip and posterior-side clip. The IB reference volume receiving 50% of the prescribed dose (IB-V_{50}) was calculated. The homogeneity index (HI) was defined as the ratio of maximum dose

Table 1 DVH constraints for planning

IB reference	≤60%	≥50% of the prescribed dose	IB-V50 ≤60%
	≤35%	≥100% of the prescribed dose	IB-V100 ≤35%
Contralateral breast	Any point	≤3% of the prescribed dose	0.9 Gy
Ipsilateral lung	≤15%	≥30% of the prescribed dose	V30 ≤15%
Contralateral lung	≤15%	≥5% of the prescribed dose	V5 ≤15%
Heart			
Right-sided lesions	≤5%	≥5% of the prescribed dose	V5 ≤5%
Left-sided lesions	≤40%	≥5% of the prescribed dose	V5 ≤40%
Thyroid	Any point	≤3% of the prescribed dose	0.9 Gy

Abbreviations: DVH = dose–volume histogram; IB = ipsilateral breast.

of PTV_EVAL to minimum dose of PTV_EVAL. The conformity index (CI) was defined as the ratio of volume that was covered by the minimal dose of PTV_EVAL to the volume of PTV. The associations between categorical variables (*e.g.*, site of IB) and patient and tumor characteristics at baseline were analyzed using Fisher's two-tailed exact test. Statistically significant differences between two sample means and medians for continuous variables (*e.g.*, IB reference volume) were analyzed using the Student's unpaired *t*-test. A p value of less than 0.05 was considered statistically significant. Multivariate analysis of prognostic factors was performed with the Cox proportional hazards model. Statistical analyses were performed with JMP software, version 5.1 (SAS Institute, Cary, NC).

Results

Outcome of 3D-CRT planning

Median IB reference volume of all patients was 824 cm^3 (range, 425–1868) (Table 2). Median right IB reference volume was 794 cm^3 (range, 463–1556) and the left IB reference volume was 849 cm^3 (range, 425–1868), respectively ($p = 0.63$). Median CCD and APD for all patients were 4.5 cm (range, 2.0–9.5) and 4.2 cm (range, 0.8–7.6), respectively.

Median CTV for all patients was 56.3 cm^3 (range, 11.3–83.6), and median PTV for all patients was 246.9 cm^3 (range, 113.4–370.9) (Table 3). The median ratio between IB-PTV and IB reference volume was 74.9% (range, 54.0–86.9). The number of external beams ranged from three to six; the four-beam technique was mainly used for patients with the right breast region, and the five-beam technique was mainly used for patients with the left breast region. The median value of mean dose of PTV_EVAL was 30.2 Gy (range, 29.5–30.8). The median value of HI for all patients was 1.24 (range, 1.14–1.39), and the median value of CI for all patients was 1.38 (range, 1.01–2.40).

Unsuitable patients for the NSABP B-39/RTOG 0413 protocol

DVH constraints for organs at risk according to the NSABP B-39/RTOG 0413 protocol were satisfied in 39 patients (78%). Seven patients showed nonoptimal DVH for the ipsilateral lung; 5 patients for the contralateral breast; 4 patients for IB-V_{50}; 2 patients for the heart; and 1 patient for the thyroid. Univariate logistic regression analysis revealed that long CCD and medial tumors were correlated with nonoptimal DVH constraints ($p < 0.0001$ and $p = 0.007$, respectively), but pathological T stage excluding pTis (T1a/T1b/T1c/T2), APD, site of IB (right/left), and IB reference volume were not ($p = 0.98$, $p = 0.54$, $p = 0.73$, and

Table 2 Patients characteristics

				Univariate analysis
	All patients ($n = 50$)	Optimal DVH ($n = 39$)	Nonoptimal DVH ($n = 11$)	p value
Pathological T stage				
pTis/pT1/pT2	12/31/7	10/24/5	2/7/2	0.82
pT1a/pT1b/pT1c/pT2*	5/5/20/7	4/4/15/5	1/1/5/2	0.98
Site of IB				
Right/left	25/25	20/19	5/6	0.73
Location of tumor				
Mediolateral	19/31	11/28	8/3	0.007
IB reference volume (cm^3)				
Median (range)	824 (425–1868)	828 (425–1868)	725 (528–1032)	0.10
CCD (cm)				
Median (range)	4.5 (2.0–9.5)	3.5 (2.0–5.5)	6.0 (4.5–9.5)	<0.0001
APD (cm)				
Median (range)	4.2 (0.8–7.6)	4.2 (0.8–7.6)	4.6 (1.0–7.5)	0.54

Abbreviations: APD = anteroposterior clip distance; CCD = craniocaudal clip distance; DVH = dose–volume histogram; IB = Ipsilateral breast.
* 1 patient was not classified according to subcategory of pathological T stage.

Table 3 Dosimetric characteristics

Dosimetric characteristics	Mean	Median	Range
CTV (cm^3)	55.5	56.3	11.3–83.6
PTV (cm^3)	247.4	246.9	113.4–370.9
IB–PTV/IB reference (%)	74.3	74.9	54.0–86.9
IB-V_{100} (%)	12.7	12.5	5.6–23.4
IB-V_{95} (%)	24.7	24.6	14.6–44.8
IB-V_{50} (%)	48.6	49.0	31.4–68.6
Ipsilateral mean lung dose (Gy)	4.1	4.2	1.2–7.6
Ipsilateral lung-$V_{9\ Gy}$ (%)	12.5	12.6	3.6–23.1
Contralateral lung-$V_{1.5\ Gy}$ (%)	0.3	0	0–10.1
Heart-$V_{15\ Gy}$ (%)	1.0	0	0–7.4
Heart-$V_{6\ Gy}$ (%)	2.7	0	0–17.1
Thyroid-$V_{0.9\ Gy}$ (%)	0.5	0	0–25.5
Contralateral breast-$V_{0.9\ Gy}$ (%)	0.1	0	0–3.6
Mean dose of PTV_EVAL (Gy)	30.2	30.2	29.5–30.8
PTV_EVAL-$V_{27\ Gy}$ (%)	99.4	99.7	96.2–100
Homogeneity index	1.23	1.24	1.14–1.39
Conformity index	1.45	1.38	1.01–2.40

Abbreviations: CTV = clinical target volume; IB = ipsilateral breast; PTV = planning target volume; PTV_EVAL = volume of PTV for evaluation.

$p = 0.10$, respectively). Multivariate analysis revealed that only a long CCD was correlated with nonoptimal DVH constraints ($p = 0.02$). DVH constraints were satisfied in only 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD (<5.5 cm) ($p < 0.0001$) (Fig. 1). Of the 2 patients with a short CCD (<5.5 cm), 1 patient with a left upper-inner primary tumor and a 5-cm CCD, did not satisfy optimal DVH for the ipsilateral lung and contralateral breast, and the other patient, who had a right upper-outer primary tumor and a 4.5-cm CCD, did not satisfy optimal DVH for the heart and IB-V_{50}. DVH constraints were satisfied in 52% of patients with a long CCD (≥5.0 cm) and 93% of those with a short CCD (<5.0 cm) ($p = 0.0007$). DVH constraints were satisfied in 0% of patients with a long CCD (≥6.0 cm) and in 90% of those with a short CCD (<6.0 cm) ($p < 0.0001$). A long CCD was correlated with not only nonoptimal DVH constraints, but also a large ipsilateral mean lung dose (MLD) ($r = 0.48$, $p = 0.0003$).

High-risk patients with large IB-V_{50}

Median IB-V_{50} of all patients was 49.0% (range, 31.4–68.6). Univariate logistic regression analysis revealed that long CCD ($r = 0.72$, $p < 0.0001$) and medial tumors ($p = 0.02$) were correlated with large IB-V_{50} (Fig. 2, 3). The site of the IB (right/left), pathological T stage (T1a/T1b/T1c/T2), IB reference volume, and APD were not correlated with a large IB-V_{50} ($p = 0.47$, $p = 0.92$, $p = 0.13$, $p = 0.10$, respectively). Multivariate analysis revealed that only a long CCD was correlated with large IB-V_{50} ($p < 0.0001$).

Discussion

The Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology Breast Cancer Working Group and the American Society for Radiation Oncology Health

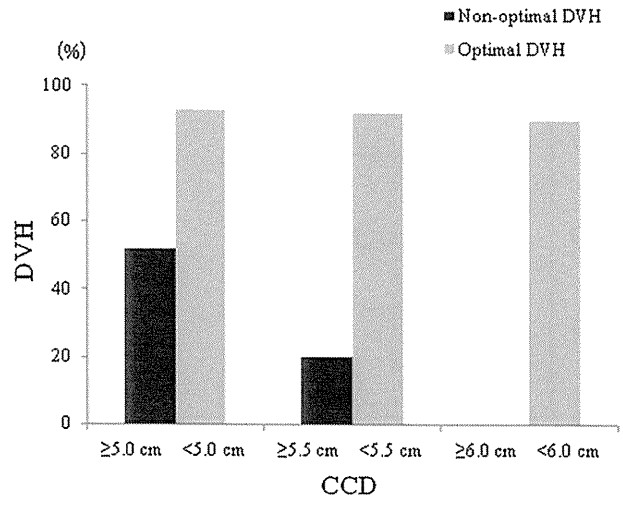

Fig. 1. Frequency of optimal and nonoptimal dose–volume histogram (DVH) constraints according to craniocaudal surgical clip distance (CCD). Left column indicates that 52% of patients with long CCD (≥5 cm) do not satisfy DVH constraints, whereas the center and right columns show that only a few patients with long CCD of ≥5.5 cm and those with long CCD of ≥6.0 cm do not satisfy DVH constraints.

Services Research Committee proposed the patient selection criteria for use of APBI based on available clinical evidence complemented by expert opinion (13, 14). The main eligibility criteria proposed by these task groups included patient age (≥60 years), pathological tumor size (≤3 cm), negative surgical margin, unicentric lesion, and pN0 (13, 14). These recommendations were mainly based on the probability of breast recurrence after APBI. To maintain the efficacy and safety of APBI, potential risk for late severe toxicities should be considered in addition to the probability of breast recurrence. The NSABP B-39/RTOG 0413 protocol requires that the ratio of lumpectomy cavity to IB volume must be <30% based on postoperative/prerandomization CT

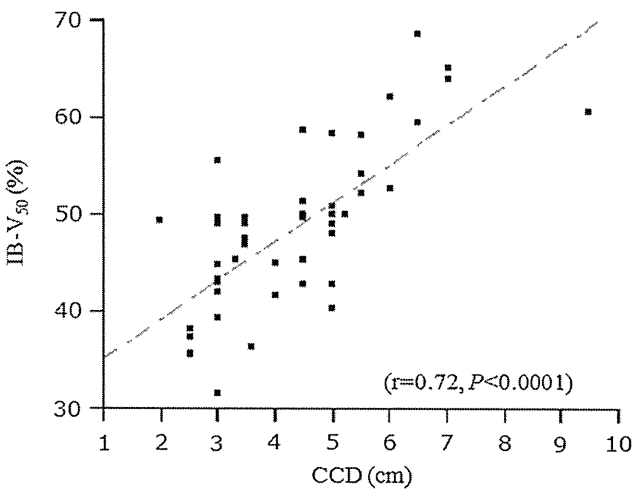

Fig. 2. Scatter plots for craniocaudal surgical clip distance (CCD) and ipsilateral breast reference volume receiving ≥50% of the prescribed dose (IB-V_{50}). Long CCD was strongly correlated with large IB-V_{50} ($r = 0.72$). IB-V_{50}. The dotted line indicates the fitting line.

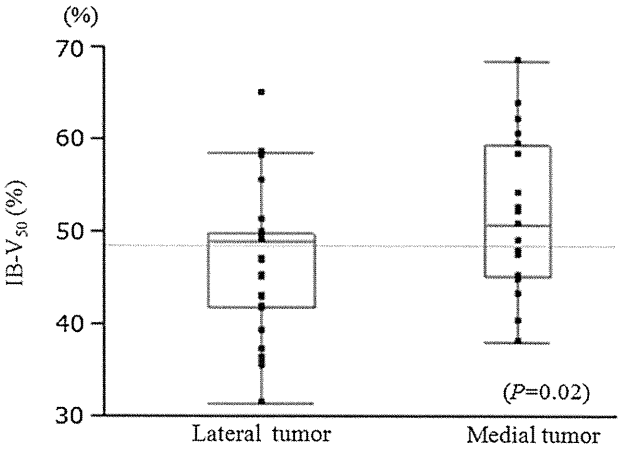

Fig. 3. Box plots for tumor location (lateromedial) and ipsilateral breast reference volume receiving ≥50% of the prescribed dose (IB-V_{50}). The gray line indicates the median value of IB-V_{50}.

imaging (9). Unfortunately, the ratio of lumpectomy cavity to IB volume and that of PTV to IB reference volume are not calculated until the RTP system operation. Thus, eligibility criteria that require complex calculations serve as obstacles toward seamless execution of clinical trials. In the majority of contemporary APBI series, patients for whom the maximal tumor size is less than 3 cm have been eligible (5, 14). In our study, pathological T stage (pT1a/pT1b/pT1c/pT2), which was classified according to pathological maximum diameter of the invasive carcinoma component, was not associated with nonoptimal DVH constraints of the NSABP B-39/RTOG 0413 protocol. Some likely explanations for this are that the pathological T stage does not include the noninvasive carcinoma component and that it does not correlate with specimen shape (*e.g.*, fan shape, slender oval) or the direction of the long axis of the specimen. On the other hand, the distance of surgical clips is directly associated with the size of the resected specimen, and the CCD strongly correlated with the field length in the craniocaudal direction and the breast irradiated volume. Distances between surgical clips are easy to measure with digital chest X-rays rather than the RTP system operation and they serve as tools to help predict which patients are unsuitable for 3D-CRT APBI. However, APD was not closely correlated with either nonoptimal DVH constraints or large IB-V_{50}. We applied the noncoplanar beam technique using tangential beam with a 10–20° steeper gantry angle and couch angles of 0–30°. With this technique, the gantry angle arrangement allows one to reduce the field width in the anteroposterior direction and the irradiated volume, in which case APD does not correlate closely with field size, irradiated volume, or nonoptimal DVH constraints.

Hepel *et al.* reported that high-, intermediate-, and low-dose volumes (IB-V_5–IB-V_{80}) all correlated with incidence of breast fibrosis after 3D-CRT APBI (7). Improved target coverage with external beam techniques comes at the cost of a higher integral dose to the remaining normal breast. With the 3D-CRT APBI technique, the volume of high-dose region (*e.g.*, IB-V_{100}, IB-V_{80}) and that of low-dose region (*e.g.*, IB-V_2, IB-V_{20}) are closely related. Jagsi *et al.* reported on the unacceptable cosmesis that developed in 7 patients among 34 patients after APBI using Intensity-modulated radiotherapy, noting that IB-V_{50} and IB-V_{100} correlated with cosmetic outcome (8). They indicated that there seemed to be a possible threshold at 40%, in which the 5 of 10 patients (50%) with an IB-V_{50} >40% experienced unacceptable cosmesis vs. the 2 of 22 (9%) below that threshold who experienced it ($p = 0.02$). On the other hand, Formenti *et al.* reported good cosmetic outcomes in most patients after performing APBI with the 3D-CRT technique in a prone position with 30 Gy in five fractions, noting that IB-V_{50} ranged from 23 to 75%, and IB-V_{100} ranged from 10 to 45% (12). In our simulation study, median IB-V_{50} of patients with optimal DVH constraints was 46.9% (31.4–58.1), and that for patients with nonoptimal DVH constraints was 59.4% (49.9–68.6) ($p < 0.0001$, data not shown). The appropriate threshold of IB-V_{50} and that of other parameters (*e.g.*, IB-V_{20}, IB-V_{80}, maximum dose) as predictive factors of late soft tissue toxicities has yet to be clarified. Further studies should be conducted to clarify predictive factors for late soft tissue toxicities.

Recht *et al.* reported that the risk of pneumonitis appeared to be related to the irradiated ipsilateral lung volume treated, and recommended that ipsilateral lung volume receiving 20 Gy or higher should be lower than 3%, and that receiving 5 Gy lower than 20% (6). They indicated that relatively low-dose lung irradiation might better help to determine the risk of pneumonitis after radiotherapy. In our study, a long CCD was correlated with large ipsilateral MLD ($r = 0.48$, $p = 0.0003$), and ipsilateral lung volume receiving 6 Gy or higher (≥20% of the prescribed dose) ($r = 0.63$, $p < 0.0001$).

A limitation of the present study was that we used simulation data rather than clinical outcomes. A prospective clinical trial should be conducted to evaluate the utility of these eligibility criteria and treatment outcomes. In addition, we could not verify the geometric couch and gantry angle limitations for the Varian linear accelerator in all patients. However, before the beginning of this study, we did verify the geometric couch and gantry angle limitations using a human-body phantom placed on a couch.

Conclusions

Patients with a long CCD, especially 5.5 cm or longer, might be unsuitable for 3D-CRT APBI from nonoptimal DVH constraints and large IB-V_{50}. Pathological T stage, APD, site of IB (right/left), tumor location (medial/lateral), and IB reference volume could not predict whether patients were unsuitable for 3D-CRT APBI.

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外科療法

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CQ 9 乳房切除術後の放射線療法は勧められるか

背景・目的

複数のランダム化比較試験とメタアナリシスにより，乳房切除術後の放射線療法が局所領域リンパ節再発率を低下させるのみならず生存率を向上させることが示された。乳房切除術後の放射線療法が再発率および生存率に与える影響を，十分な経過観察が行われた臨床試験の結果を中心に評価する。

9-a 腋窩リンパ節転移4個以上陽性の患者では乳房切除術後の放射線療法が勧められるか

推奨グレード A

腋窩リンパ節転移4個以上の患者では乳房切除術後の放射線療法が強く勧められる。

解説

1990年代後半に報告された高リスク患者(腋窩リンパ節転移陽性や原発巣の最大径が5 cm以上など)を対象とした3つのランダム化比較試験において，乳房切除術後の放射線療法が局所領域リンパ節再発を1/3～1/4に減少させるのみならず生存率を向上させることが示された[1)～4)]。乳房切除術を施行した腋窩リンパ節転移陽性の8,505例を対象としたEBCTCGによるメタアナリシスの結果からも，術後照射により5年局所領域リンパ節再発率が23%から6% (17%の減少)に減少することが示された[5)]。また，36のランダム化比較試験をまとめたメタアナリシス(13,199例)の結果でも，照射を行わなかった場合に比して術後照射は局所領域リンパ節再発の相対リスクを70～80%減少させることが示された[6)]。

閉経前患者を対象としたDanish 82bと閉経後患者を対象としたDanish 82cを統合解析した結果，腋窩リンパ節転移4個以上陽性の患者では術後照射により生存率が改善することが示された(15年全生存率21% vs 12%，$p=0.03$，リスク減少比0.49，95%CI：0.31-0.76)[7)]。ASCOやACR，NCCN，カナダのガイドラインでも，腋窩リンパ節転移4個以上陽性の患者に対しては乳房切除術後の放射線療法を行うことが強く推奨されている[8)～11)]。

⑨-b 腋窩リンパ節転移1～3個陽性の患者では乳房切除術後の放射線療法が勧められるか

推奨グレード B　腋窩リンパ節転移1～3個の患者にも乳房切除術後の放射線療法が勧められる。

解説

1990年代後半に報告された3つのランダム化比較試験に登録された患者の約60%は腋窩リンパ節転移数が1～3個の患者であった[1)～4)]。デンマークの比較試験は郭清されたリンパ節数がやや少なく陽性リンパ節数の精度に問題があるとの批判はあるが，Danish 82b と Danish 82c とを統合解析した結果では，腋窩リンパ節数1～3個陽性の患者においても術後照射は全生存率を改善させることが示された(15年全生存率57% vs 48%，$p=0.03$，リスク減少比0.69，95%CI：0.50-0.97)[7)]。一方，20年経過観察を行ったカナダの比較試験のサブセット解析では，疾患特異的生存率は術後照射を行うことで有意に改善したが(20年疾患特異的生存率57% vs 41%，リスク減少比0.64，95%CI：0.42-0.97)，全生存率に関しては統計学的有意差を認めなかった(20年全生存率57% vs 50%，リスク減少比0.76，95%CI：0.50-1.15)[4)]。後ろ向き研究ではあるが，摘出リンパ節数における転移リンパ節数の割合，ホルモン受容体や HER2 の発現状況などのバイオマーカーを加えた術後照射の意義が検討されており，さらなる研究が期待される[12)～14)]。ASCO やカナダのガイドラインでは腋窩リンパ節数1～3個陽性の患者に対して術後照射を行うべきかに関しての結論は出ていないとしているものの，NCCN ガイドラインでは術後照射を行うことを強く考慮すべきとしている[8)11)15)]。いまだ統一した見解は得られていないが[10)]，前二者のガイドラインの公表後に報告されたデンマークの統合解析の結果やカナダの比較試験の長期経過後に行ったサブセット解析の結果より，腋窩リンパ節数1～3個陽性の患者に対しても術後照射を考慮すべきである。

原発巣の最大径が5 cm 以上で腋窩リンパ節転移陰性の患者は乳癌全体の0.3%程度と稀であり，乳房切除後の術後照射の臨床的意義を検証することは困難である[16)]。後ろ向き研究やがん登録のデータを用いた報告があるが，一定の見解は得られていない[16)～18)]。

検索式・参考にした二次資料

2008年版での検索結果に加え，PubMed で，Breast Neoplasms/radiotherapy，Mastectomy，Breast Neoplasms/surgery のキーワードを用いて検索した。検索期間は2008～2011年とした。また，他のガイドラインや二次資料などから重要と思われる文献を採用した。

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CQ 10 乳房切除術後の放射線療法における適切な照射法は何か

背景・目的

乳房切除術後の放射線療法は局所領域リンパ節再発率の低下と生存率の向上をもたらす。しかし，不適切な照射技術は生存率を向上させないばかりでなく，心筋障害などの晩期有害事象を増加させる可能性がある。照射技術が治療成績や毒性に与える影響を評価する。

10-a 乳房切除術後の放射線療法では胸壁を照射野に含めることが勧められるか

推奨グレード A　乳房切除術後の放射線療法では胸壁を照射野に含めることが強く勧められる。

解説

術後照射を行わない場合の局所領域リンパ節再発の部位としては，胸壁および鎖骨上窩が多く，術後照射として胸壁を照射野に含めることに対する異論は少ない[1)~6)]。術後照射の有効性を検証した36のランダム化比較試験を対象としたメタアナリシスにより，照射野に胸壁，腋窩，鎖骨上（±胸骨傍リンパ節）を含め，かつ放射線生物学的効果として2 Gy/回換算で総線量40~60 Gy相当の線量が用いられた場合には，術後照射は局所領域リンパ節再発，乳癌による死亡，全生存のすべてを有意に改善させることが示された（10年経過観察時の死亡リスクのオッズ比0.78, 95%CI：0.70-0.85, $p<0.001$）[1)]。

総線量，1回線量，ボーラス材の使用，術創部への追加照射などに関するランダム化比較試験は存在せず，信頼性の高い情報は少ない[4)6)~9)]。NCCNやACRのコンセンサスパネルでは通常分割照射法で1回線量1.8~2.0 Gy，総線量50~50.4 Gyを投与することを推奨している[6)10)]。切除断端陽性例などでは，1回線量2.0 Gyで計10 Gy程度が追加照射される。胸壁の皮膚への線量を適切なものにするため6 MV以上の高いエネルギーX線を用いる場合にはボーラス材を使用することが，ACRのエキスパートパネルにより推奨されている[6)]。晩期有害事象を軽減させるために，三次元治療計画装置を用いて心臓や肺への線量を慎重に検討することが重要である。

1週間以上の休止期間が治療成績の低下をきたすとの後ろ向き報告があるが，休止期間の臨床的意義を臨床試験で検証することは困難である[11)]。日常臨床では対応可能な範囲で総治療期間が延長しないよう考慮する。全身化学療法と放射線療法の至適タイミングに関しても十分な情報はないが[6)]，腋窩リンパ節転移例が中心のため日常臨床では化学療法が先行される。

10-b 乳房切除術後の放射線療法では鎖骨上リンパ節領域を照射野に含めることが勧められるか

推奨グレード B 乳房切除術後の放射線療法では鎖骨上窩リンパ節領域を照射野に含めることが勧められる。

解説

術後照射を行わない場合の局所領域リンパ節再発の部位としては，胸壁に次いで鎖骨上窩への再発が多い[2)3)6)]。鎖骨上窩への照射の意義を検証した試験は存在しないが，生存率の向上を示した試験では胸壁に加え鎖骨上窩への照射を行っている[12)~15)]。ASCOのガイドラインおよびACRのコンセンサスパネルでは鎖骨上窩への照射を推奨している[4)~6)10)]。線量は，胸壁照射と同様に1回線量1.8～2.0 Gy，総線量50～50.4 Gyを投与する[6)]。三次元治療計画装置を用いて患者個々の体型や解剖学的位置関係を考慮した放射線療法を行うことが重要であり，個々の患者で病理所見や術式から含めるべきリンパ節領域が十分かを把握しておく必要がある[6)]。

術後照射を行わない場合でも胸骨傍リンパ節再発の頻度は低い。生存率の向上を示したランダム化比較試験では胸骨傍リンパ節を照射野に含めているが，同部位への照射の意義に関しては一定の見解は得られていない[1)7)16)]。

検索式・参考にした二次資料

2008年版での検索結果に加え，PubMedで，Breast Neoplasms/radiotherapy，Mastectomy，Thoracic Wall，supraclavic*lymph node*，Breast Neoplasms/surgery，Postmastectomyのキーワードを用いて検索した。検索期間は2008～2011年とした。また，他のガイドラインや二次資料などから重要と思われる文献を採用した。

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