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BRIEF ARTICLE

Assessment of contralateral mammary gland dose in the treatment of breast cancer using accelerated hypofractionated radiotherapy

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Abstract

AIM: To measure the dose distribution, related to the treatment planning calculations, in the contralateral mammary gland of breast cancer patients treated with accelerated hypofractionated 3-dimensional conformal radiotherapy.

METHODS: Thirty-four prospectively selected female patients with right breast cancer (pN0, negative surgical margins) were treated with breast-conserving surgery. A total dose of 42.5 Gy (2.66 Gy/fraction) was prescribed; it was requested that planning target volumes be covered by the 95% isodose line. The contralateral mammary gland was defined on CT simulation. The dose received was evaluated by dose volume histograms.

RESULTS: The measured contralateral breast doses were: (1) Dose maximum: 290-448 cGy [Equivalent (Eq) 337-522 cGy]; (2) Mean dose: 45-70 cGy (Eq 524-815 cGy); and (3) Median dose: 29-47 cGy (337-547 cGy) for total primary breast dose of 42.5 Gy in 16 equal fractions. The spearman rho correlation showed statistical significance between the contralateral breast volume and maximum dose (P = 0.0292), as well as mean dose (P = 0.0025) and median dose (P = 0.046) to the breast.

CONCLUSION: Minimizing the dose to the contralateral breast has to be one of the priorities of the radiation oncologist when using short schedules because of the radiosensitivity of this organ at risk. Further study is necessary to assess the long-term clinical impact of this schedule.

Key words: Breast cancer; Hypofractionation; Contralateral breast; Dose calculation

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INTRODUCTION

Breast cancer is the most common (excluding skin) malignant neoplasm among women. In the United States, it was calculated to have an approximate lifetime risk of 13.4%; 184 450 cases are invasive and 67 770 cases are *in situ* carcinomas per year[1].

The purpose of radiation treatment following lumpectomy is to improve local control in the treated breast with as little toxicity as possible. Since radiation therapy efficacy has improved, the issues related to post-therapy complications have become very important. Contralateral breast dose from primary breast irradiation has been implicated in the risk of second breast malignancies.

Daily treatment over several weeks can be very inconvenient to many patients. A high number of studies[2-13] have shown that the goal of post-lumpectomy radiotherapy is also achieved with shorter than the conventional fractionation schedules. Whole breast radiotherapy for invasive breast cancer demonstrates equivalent efficacy and morbidity for conventional and hypofractionated treatment, as shown in a Canadian trial involving 1234 women with node-negative breast cancer and clear margins of excision after breast conserving surgery and axillary dissection. Women were randomly assigned to receive whole breast irradiation of 42.5 Gy in 16 fractions over 22 d (short arm) or 50 Gy in 25 fractions over 35 d (long arm).

Hypofractionation can increase the late normal tissue damage. The principal long-term effects that impair cosmesis are fibrosis and atrophy of the breast which are a result of the specific response of fibrocytes to irradiation.

The aim of the present study was to evaluate the delivery of accelerated hypofractionated 3-D conformal radiotherapy (3D-CRT) in the contralateral mammary gland in breast cancer patients.

MATERIALS AND METHODS

Patient selection

Between October 2009 and September 2010, 34 women with a primary diagnosis of invasive carcinoma were enrolled in the treatment protocol. In the study were included patients > 50 years old, diagnosed with stage Ⅰ-Ⅱ, right-sided breast cancer. Large mammary glands with a distance from sternum to mid axillary line more than 25 cm were excluded from the study.

All patients underwent breast-conserving surgery (with axillary sampling or dissection). In particular, they had a lumpectomy before radiotherapy. They had no adjuvant chemotherapy. Exclusion criteria included previous treatment for a diagnosis of ductal carcinoma *in situ* or invasive breast carcinoma, omission of post-operative radiation, or surgical management with mastectomy.

Pathological results were abstracted from the original histopathology report. The specimens showed an invasive adenocarcinoma, non-high grade, negative margins (> 2 mm), no axillary lymph nodes involved.

Simulation

Each patient underwent a virtual CT-simulation, in supine position, using dedicated devices. The patient's arms were raised above the head using an arm support in carbon fiber (Sinmed©, Reeuwijk, The Netherlands).

Planning CT scans

For treatment planning, a CT scan covering a region from the 6th cervical vertebra to the middle part of the abdomen was obtained for each patient. The patients were scanned with 5 mm slice thickness in simulation CT scan and the CT datasets were transferred to the Prosoma® Treatment Planning System through the DICOM network.

Contouring organs at risk and planning target volume

All contouring of target volumes and normal structures [organs at risk (OARs)] were performed in the Prosoma Treatment Planning System. The following structures were delineated: clinical target volume (CTV), planning target volume (PTV), ipsilateral, contralateral lungs and contralateral breast. According to the ICRU[14,15], OAR is defined to be an uninvolved organ that, if given an excess radiation dose, might be damaged and would compromise the success of the course of radiation therapy.

The demonstrable tumor plus the microscopic disease constitute the CTV.

Margins are needed to surround the CTV to ensure that the CTV lies within the treatment field during the entire course of radiation therapy. These internal margins, in addition to the CTV, constitute the internal target volume (ITV).

In order to account for setup uncertainties, one adds a setup margin to the ITV to generate a PTV.

The CTV, PTV and OARs were outlined on all CT slices. The CTV was expanded to a PTV with 5 mm, with a constraint reverse expansion of 4 mm to the skin surface to avoid potential skin toxicity[16,17]. The PTV provided a margin around the CTV to compensate for the variability of treatment setup and motion of the breast or chest with breathing[17].

Dose prescription

The patients were treated with adjuvant whole breast radiotherapy and they received no boost and no supraclavicular irradiation. Radiation therapy to the involved breast was planned to be administered within 12 wk of the most recent surgery. A dose of 42.5 Gy was delivered in 16 daily fractions over 3.5 wk (2.66 Gy/fraction, based on the Canadian randomized trial)[2,3]. Breast radiation was delivered using tangential fields to the entire breast and underlying chest wall, as previously described. The prescription dose of 42.5 Gy was defined for the 95% isodoses of the PTV. In particular, 95% of the PTV should have been covered within 95%-110% of the prescribed dose (39.9-46.2 Gy). Partial wedging or dynamic (Multi Leaf Collimator-MLC) was employed to improve dose homogeneity (7%). To evaluate the dose constraints

for normal tissues we used the Toxicity criteria of the Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) NSABP B-39/RTOG 0413 protocol[18] corrected for hypofractionation, taking into account potential unfavorable anatomy[19]. The dose constraints for the OARs are described below: ipsilateral lung (without supraclavicular irradiation): V25 Gy < 5%, V17 Gy < 8%, V8 Gy < 10%, mean dose < 6.36 Gy; contralateral lung: V2.5 Gy < 15%; contralateral breast: dose max < 3% of the prescribed dose, mean dose as low as possible.

Conventional planning

For the conventional technique, we used a virtual simulation. The entire breast was treated, using a parallel pair of two opposed tangential fields. Weighted beams and wedges were used as necessary. The fields were placed isocentrically, with matching posterior field borders. Dose calculation was performed and normalized to isocenter. The prescribed dose was 42.5 Gy delivered in 16 daily fractions, in whole-breast, given in 2.66 Gy fractions with accelerated hypofractionated 3D-CRT[20].

The treatment planning was performed in the Eclipse™ (Varian Medical Systems, United States) TPS. This treatment planning system includes the Pencil Beam algorithm for dose calculation. The beam arrangement consisted of 2 tangential beams, where the beam angles, apertures, weights and dynamic wedges were optimized by standard, forward planning. The photon beam energy was 6 MV, using the linear accelerator VARIAN 600C. To account for the tumor movement during treatment, 2 cm was extended beyond the skin surface in the anterior direction using the skin flash tool in the treatment planning system.

For the treatment technique, histograms of the contralateral breast were generated; a number of parameters, including mean, median and maximum dose to the breast, were evaluated.

Clinical examination

During the radiation treatment the patients were monitored every week. Post treatment management included adjuvant endocrine therapy according to the National Comprehensive Cancer Network Guidelines. After the completion of the treatment, the patients were evaluated by a radiation oncologist every 3 mo. Acute skin and breast tissue reactions were also recorded. Toxicity was defined according to the RTOG/EORTC acute and late radiation morbidity scoring system[21].

Statistical analysis

Correlation of numerical variables was investigated by Pearson correlation coefficient. The whole analysis was performed by using the SPSS version 10 (Chicago, IL).

RESULTS

Thirty-four eligible women treated with adjuvant radiation following breast-conserving surgery were analyzed. The median age of the patients at the time of radiation was 65 years (range, 51-79 years). All patients underwent breast-conserving surgery with accompanying axillary sampling or dissection. All completed adjuvant whole breast radiotherapy with hypofractionated schedule (42.5 Gy in 16 fractions). Clinical and pathological characteristics were similar among the patients.

Table 1 Contralateral breast treatment characteristics

Treatment characteristics	Range
Dose max	290-448 cGy
Mean dose	45-70 cGy
Median dose	29-47 cGy
Monitor units	199-217
Breast volume	749-1474 cm^3

Table 2 Statistical analysis

Correlation	Spearman rho	*P* value
Breast volume *vs* max dose to the breast	0.0090	0.0292
Breast volume *vs* mean dose to the breast	0.0153	0.0025
Breast volume *vs* median dose to the breast	0.0028	0.046
Breast volume *vs* gantry angle	0.0042	0.2195

The doses to the opposite breast were generated from the dose volume histograms (DVHs) (Table 1). The doses represent the combined contribution from both the medial and lateral tangential beams. An isocentric technique was used for treatment. Scatter dose from the medial tangential field to the contralateral breast originates in the accelerator head and its accessories. The use of a medial wedge increased the contralateral breast dose due to an increase in scattered photons and in monitor units. The wedge angle used in our study ranged between 15° and 30°. For total primary dose of 4256 cGy, the measured dose maximum at the contralateral gland varies from 290-448 cGy. The mean dose varies from 45 to 70 cGy. The median dose was between 29-47 cGy. The average volume of the breast for the patients in question was 856 ± 327 cm^3. The monitor units obtained from the pencil beam calculations and used for the treatment were in the range from 199 to 217. A representative dose distribution for the breast with the contralateral breast contouring is shown in Figure 1 with regard to axial and coronal planes. A representative cumulative dose volume histogram is shown in Figure 2. The spearman rho correlation showed statistical significance between the contralateral breast volume and maximum dose ($P = 0.0292$), as well as mean dose ($P = 0.0025$) and median dose ($P = 0.046$) to the breast (Table 2). Received doses in detail as extracted from DVHs are shown in Table 3.

DISCUSSION

The choice of treatment for breast cancer is usually determined by tumor stage, patient age, co-morbidity, as well as by patient preferences. The long duration of treat-

Table 3 Calculated doses, breast volume and monitor units in details

No.	Age (yr)	Breast volume (cm^3)	Breast dose (cGy)			
			Max	Mean	Median	MU
1	79	1474	348	49	31	217
2	55	1090	380	45	41	209
3	63	803	367	54	47	203
4	61	749	290	45	35	199
5	71	789	448	63	46	203
6	56	857	345	56	36	204
7	67	942	401	47	32	210
8	72	801	412	52	39	200
9	61	998	434	51	40	202
10	56	796	399	52	45	210
11	58	893	387	45	33	199
12	72	956	402	70	33	204
13	71	1001	345	55	41	207
14	79	842	204	49	39	204
15	64	865	341	51	38	207
16	57	789	296	57	40	209
17	66	985	356	68	32	205
18	73	934	298	54	30	209
19	75	924	304	57	39	200
20	76	1023	326	61	45	210
21	59	1031	348	49	42	210
22	52	1320	401	51	40	211
23	57	980	295	59	32	205
24	58	1002	432	57	34	206
25	74	1007	422	49	37	209
26	70	983	427	61	40	200
27	60	879	346	58	40	204
28	74	765	307	49	38	214
29	68	795	401	60	39	208
30	72	1021	397	50	32	201
31	70	784	350	63	29	205
32	59	788	386	57	36	201
33	62	901	409	55	42	209
34	67	854	297	70	45	202

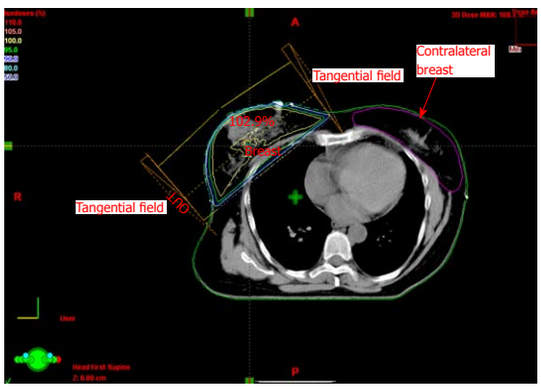

Figure 1 Representative dose distribution for the breast with the contralateral breast contouring.

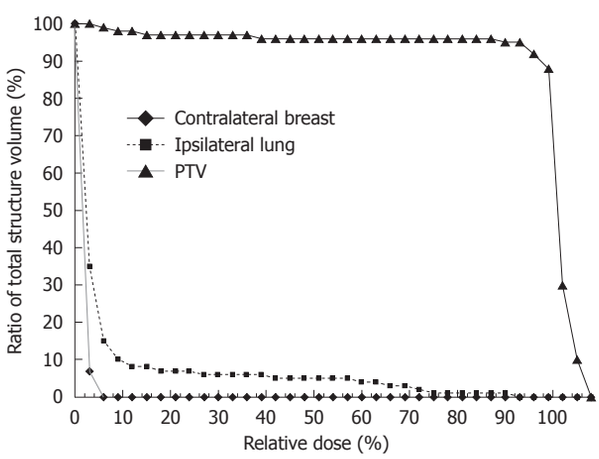

Figure 2 Representative cumulative dose volume histogram.

ment can adversely affect the quality of a patient's life. The drawbacks of a prolonged schedule include inconvenience, loss of earnings and cost of traveling for 5 wk, which can be significant for many women[22]. Shorter schedules, typically delivering a lower total dose in fewer, but larger than 2 Gy fractions, are more convenient for the patients by limiting the number of treatment attendances. Moreover, the reduced resource use in terms of personnel and machine time is advantageous for radiotherapy departments and translates into lower treatment costs. In order to formally validate this therapeutic approach from a societal perspective, however, cost-effectiveness evaluations weighing long-term outcome against the societal costs incurred for many years after treatment are needed[5,6,22]. The efficacy of this schedule has been analyzed by Whelan *et al*[2,3] and seems to be associated with no difference in 10-year LR (6.2% *vs* 6.7%, respectively), DFS, OS, or good/excellent cosmetic outcome (70% *vs* 71%).

In the linear quadratic model, fractionation sensitivity is expressed by the parameter α/β. If α/β is low (e.g., 1 Gy) the tissue is much more sensitive to increasing dose per fraction than if α/β is high (e.g., 10 Gy), while cancerous tissues generally have rather high α/β ratios[20].

After the report of Yarnold *et al*[23] in patients irradiated following breast-conserving surgery with the standard 25 fractions or a 13-fraction radiotherapy scheme, it appears reasonable to use an α/β around 3 Gy in developing fractionation schedules for breast irradiation, which are iso-effective regarding overall late normal tissue effects. Although this study had insufficient statistical power to reliably determine the fractionation sensitivity of breast cancer, tentative results from the trial suggest that the α/β ratios are comparable for both breast fibrosis and local control endpoints. In the past, α/β values of 4-5 Gy have been derived for the radiation response of recurrent or inoperable breast cancer[24,25].

Moreover, an α/β ratio of 4 has been reported for human breast carcinoma cell lines[26-28].

3D-CRT and intensity modulated radiotherapy (IMRT) have allowed more conformal dose distributions to the breast, while selectively sparing surrounding normal tissues. During external beam radiotherapy, the contralateral breast receives radiation due to leakage from the collimator and scatter from primary irradiation[29]. Other factors that contribute to dose may include blocks, orientation of the fields, wedge size, wedge angle and the technique used for treatment[30]. Tangential fields and, if

used, the anterior supraclavicular field contribute to contralateral scatter dose.

The dose to the contralateral breast can be reduced to some extent by reducing the medial wedge angle[30,31]. The closeness of the gantry angle to the contralateral breast is also associated with increase in dose. Contralateral scatter doses are highest for patients with large protruding breasts whose isocentric treatment plan needs the use of a large wedge and higher beam energy[30].

Radiation, especially at sub-therapeutic doses, has been proven to be carcinogenic[32-37]. According to the United Nations Scientific Committee on Effects of Atomic Radiation report[38], experimental exposure of animals to radiation and observations on exposed human populations have shown that ionizing radiations are general carcinogens capable of inducing tumors in almost all tissues of mammals irrespective of species. Dose to the contralateral breast as a result of radiotherapy of breast should not be ignored in radiotherapy, and more so in patients younger than 45 years. The breast tissue is highly sensitive and therefore the contralateral breast must be regarded as an organ at risk (sensitive organ) while planning for radiotherapy. As already reported[32-39], radiotherapy-associated risk of contralateral breast cancer (CBC) increases with decreasing age at first treatment [age < 35 years, hazard ratio (HR) = 1.78, 95% CI: 0.85 to 3.72; age > 45 years, HR = 1.09, 95% CI: 0.82 to 1.45]. This is very important, particularly in women irradiated at a younger age[32-34] and among women treated under the age of 45 years. Boice *et al*[32] have shown that the incidence of radiation-induced breast cancer is a linear function of dose received, with latent periods of over 10 years. Secondary tumors following radiotherapy may be observed around or well outside the margin of the PTV[35-37]. Other important considerations include dose to OARs, including the ipsilateral and contralateral lungs.

Women treated before age 45 years with post-lumpectomy radiotherapy experience 1.5-fold increased risk of CBC compared with those who had post-mastectomy radiotherapy. The joint effects of post-lumpectomy radiotherapy and strong family history for breast cancer on risk of CBC were found to be greater than expected when individual risks were summed (HR = 3.52, 95% CI: 2.07 to 6.02, $P = 0.043$).

Accelerated hypofractionated radiotherapy is currently used because of the similar local control and toxicity rates. To our knowledge, this is the first report on the estimation of the contralateral breast dose using the hypofractionated schedule[3].

Boice *et al*[32] have conducted a case control study in a cohort of 41 109 women diagnosed with breast cancer and analyzed the records. They found mean contralateral breast dose to be 282 cGy with a maximum of 710 cGy and relative overall increase in risk of contralateral breast malignancy due to treatment of primary by radiation to be 1.19. However, the risk of a second malignancy in the contralateral breast was 1.59, significantly high, in patients who underwent radiotherapy at a younger age than 45 years for primary breast malignancy. This indicates high risk for younger patients.

Bhatnagar *et al*[40] reported a comparison of contralateral breast dose during primary breast irradiation using IMRT and conventional tangential field technique. They observed the contralateral breast dose to be 7.74% ± 2.35% of the primary breast dose (5000 cGy) in IMRT treatment planning and 9.74% ± 2.04% of primary breast dose during conventional tangential field technique, i.e. about 20% reduction in contralateral breast dose with IMRT as compared to conventional tangential treatment with wedge. In our study, the measurements are in accordance with the conventional tangential field technique of Bhatnagar *et al*[40].

Tercilla *et al*[41] measured the contralateral breast dose during half beam block and isocentric treatment techniques for patients treated with primary breast irradiation with a Cobalt^{60} unit. They measured contralateral breast dose with thermoluminescent dosimeters (TLD) in 15 patients and the doses were 325-650 cGy during half beam block tangential field treatment and 200-450 cGy without half beam block tangential field treatment for a total primary breast dose of 5040 cGy in 28 equal fractions. They recommended non-use of half beam block techniques; however, this will increase the ipsilateral lung and rib dose[29,42]. Our doses are on the high side as compared to doses reported by Tercilla *et al*[41] because we treated the chest wall using slightly wider fields.

Bhatnagar *et al*[40,43] have studied the effect of breast size on scatter dose to the contralateral breast. They treated 65 patients with breast cancer using 6 MV photon with IMRT technique and measured contralateral breast dose using TLD[44]. The primary breast size volume was calculated by the planning system from CT slices. They found a mean contralateral dose of 7.2% of the primary breast dose (5000 cGy) and found that the contribution to contralateral breast dose is strongly dependent on primary breast size of the patient. Therefore, this has become of more concern in young breast cancer patients with bulky protuberant breasts.

According to Chougule[29], the dose at the contralateral breast nipple was 152.5 to 254.75 cGy for a total primary breast dose of 5000 cGy in 25 equal fractions (Co^{60} fields), which amounted to 3.05%-6.05% of total dose to the diseased breast. Furthermore, it was observed that the maximum contribution to the contralateral breast dose was due to the medical tangential half blocked field. Again in our case, although we used a strictly conformal technique with a full 3-D treatment planning, the measurements are of a higher order than those of Chougule[29], mainly because we did not take measurements only from the nipple where very much less scattered radiation dose is expected, but from the whole contralateral breast and especially from the neighboring breast tissues.

Muller-Runkel *et al*[42] have advocated covering of the contralateral breast with a thin lead sheet to reduce the scattered contribution to contralateral breast skin, though little can be done to reduce the dose from the

lateral tangential field as the dose is caused by internal body scatter.

Using modern techniques of CRT and IMRT, the contralateral breast dose can be reduced by 10%-20% but it still is about 3.05%-6.05% (153-255 Gy) of a primary breast dose of 5000 cGy, which cannot be ignored. IMRT technique provides better dose uniformity as compared to other tangential field techniques, as well as significantly reducing the dose to the contralateral breast[40,43,44].

In a previous study, we have already reported the fine cosmesis in hypofractionated breast irradiation, as used in our institution[45]. In this report we are analyzing the dose at the contralateral breast. Further to ICRU reports[14,15], our results are in accordance with a previous study[30], showing that there are only two significant correlations concerning the contralateral breast volume and the dose. This was logical since the volume of the breast would be expected to be correlated with the incidence of direct or scattered field to be inserted. However, although in previous studies the gantry angle was correlated with higher doses to the contralateral breast[29,30,40,42-44], in our research we have not seen any significant correlation. The reason for this might be the fact that we used a smart immobilization device for the chest wall and the hands, which produces a detachment of the contralateral breast. Moreover, the majority of contralateral breast doses are from the scatter doses coming from the collimator. By using the asymmetric collimator technique, the unwanted scattering doses from the collimator can be minimized. In this current study, asymmetric collimators were used.

In terms of the dose uniformity all over the normal breast tissue (skin included), we did not used field in field techniques or a bolus in order to compensate low skin doses.

The main limitations of the present study are the small number of patients, the absence of *in vivo* dosimetry and the short follow up. Further dosimetric analysis and longer follow up are needed to evaluate the adverse late effects which could be increased because of the hypofractionation schedule used, such as for example, ischemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis. In general, when hypofractionation is used, it is advisable that both possible dose inhomogeneity and normal tissue protection should be taken into account, while the use of three-dimensional conformal techniques should be mandatory[46]. In our clinical routine practice today, further to the use of three-dimensional conformal techniques, we are continuing the study by using *in vivo* dosimetry and further results will be reported after we have evaluated a sufficient number of patients. These results stress the necessity of meticulous patient observation and long follow up to the contralateral breast.

COMMENTS

Background

Lumpectomy followed by breast irradiation is an alternative to mastectomy in early-stage breast cancer. Adjuvant whole breast radiotherapy in patients diagnosed with invasive breast cancer improves local control. Delivering postoperative radiotherapy in a shorter period of time is as effective as longer treatment regimens. Hypofractionated adjuvant radiation schedules have been commonly used in Canada and the United Kingdoms based on data from early invasive breast cancer randomized studies, showing equivalent local control, survival and morbidity rates. Contralateral breast dose from primary breast irradiation has been implicated in the risk of second breast malignancies. The probability of developing contralateral breast cancer represents a serious concern. This study was conducted to measure the dose distribution, related to the treatment planning calculations, in the contralateral mammary gland, when the affected breast was treated with accelerated hypofractionated 3-dimensional conformal radiotherapy.

Research frontiers

The hotspots or important areas in the research field related to the article are as following: (1) The use of dose volume histograms (DVH) for the assessment of the dose to the contralateral breast in a hypofractionated scheme; (2) The usefulness of the 3-dimensional conformal treatment planning technique for the accurate calculation of the dose in the organs at risk, as defined by the radiation oncologist (ipsilateral lung, contralateral breast, *etc.*).

Innovations and breakthroughs

To summarize, this is the first study dealing with the dose to the contralateral breast in a hypofractionated schedule, whereas all similar studies were concerned with the dose in the contralateral breast but under a conventional schedule (2 Gy per fraction instead of 2.66 Gy per fraction). Moreover, for the readers this article incorporates the importance of 3-dimensional treatment planning calculations.

Applications

Further application should be *in-vivo* dosimetry to the contralateral breast together with the modification of the fields (geometry and intensity modulation) for reducing the dose to the contralateral breast. Minimizing the dose to the contralateral breast has to be one of the priorities of the radiation oncologist in short schedules because of the radiosensitivity of this organ at risk. Further study is necessary to assess the long-term clinical impact of this schedule.

Terminology

DVH is the histogram displaying the function between the delivered dose and the volume of a current target or organ. Three-dimensional conformal treatment planning technique concerns the calculation of the dose in each CT plane of the irradiated area. The ICRU defines an organ at risk to be an uninvolved organ that, if given an excess radiation dose, might be damaged and which would compromise the success of the course of radiation therapy. The demonstrable tumor plus the microscopic disease constitute the clinical target volume (CTV). Margins are needed to surround the CTV to ensure that the CTV lies within the treatment field during the entire course of radiation therapy. These internal margins, in addition to the CTV, constitute the internal target volume (ITV). In order to account for setup uncertainties, one adds a setup margin to the ITV to generate a planning target volume.

Peer review

The study seems to be interesting, however there are some points to be reviewed.

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