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Scientific Article

In Silico Assessment of the Radiation Dose Range for Definitive Stereotactic Body Radiation Therapy of Primary Breast Cancer

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Purpose: The maximal dose for partial breast irradiation (PBI) with stereotactic body radiation therapy for definitive local therapy of nonmetastatic breast cancer has not been established. Here we evaluate the maximal achievable coverage of the planning target volume suitable for PBI without violating organs-at-risk constraints.

Methods and Materials: Planning computed tomography scans of 22 patients with pulmonary or cardiac risk factors and left-sided disease in prone and supine position (sp) were obtained. Plans for PBI in 5 fractions were generated according to the Guidelines of the American Society for Radiation Oncology. Maximum tolerated dose (MTD) was defined when the dose reached any constraint of a neighboring organ based on recommendations of the American Association for Physics in Medicine.

Results: Mean MTD was 45.9 ± 3.9 Gy (range, 38.8-53.9) in sp and 46.1 ±3.2 Gy (range, 37.3-53.9) in prone position (pp), respectively. The MTD was ≥44.3 Gy in sp and ≥44.8 Gy in pp in 95% of patients. Fat tissue was the dose limiting structure in 11 of 22 patients in sp and 15 of 22 in pp. D_{max} to the fat tissue reached 40.0 Gy (±3.3 Gy) in sp and pp. Skin was the dose limiting structure in 7 of 22 patients in sp and in 6 of 22 in pp. D_{max} to the skin was 30.5 Gy (±7.4 Gy) in sp and 31.0 Gy (±7.0 Gy) in pp ($P = .8$). Ribs were dose limiting in 4 of 22 patients in sp and in 1 of 22 in pp. D_{max} to the ribs was 31.4 Gy (±9.5 Gy) in sp and 21.4 Gy (±11.0 Gy) in pp ($P < .01$). D_{max} to the intraventricular artery was 3.4 Gy (±3.1 Gy) in sp and 7.5 Gy (±5.7 Gy) in pp ($P < .01$).

Conclusions: For definitive stereotactic body radiation therapy for early-stage breast cancer, we propose a dose escalation starting with 45 Gy in 5 fractions to be tested in a clinical trial. Prone position is advised for tumors close to the thoracic cage.

Introduction

Nonsurgical treatment of early-stage breast cancer with radiation therapy (RT) alone has been investigated using conventional external beam radiation therapy already 40 years ago and local control rates reported rarely exceeded

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60%.[1-3] The availability of stereotactic body radiation therapy (SBRT) allows focal dose intensification while limiting dose to surrounding tissue in almost any clinical scenario of solid tumor manifestations.[4,5] SBRT leads to local tumor control without subsequent surgery in a variety of oncological settings.[6,7] In the context of breast cancer, SBRT has been proposed for patients with inoperable breast cancer because of comorbidity for palliative therapy.[8,9]

Using preoperative RT, Albendea Roch et al[10] treated patients with 30 Gy in 5 fractions and an efficacy without any major complications in 117 patients. Bosma et al[11] observed complete response rates in > 25% of patients using a preoperative dose of 30 Gy in 5 fractions. Feasibility of a single fraction of 21 Gy preoperatively was reported by Guidolin et al.[12] However, high doses given with SBRT might enhance inflammation, necrosis, or rib fractures.[13] Thus, neighboring structures often limit the dose that can be applied safely.[14-16] The potential of eradicating early breast cancer with SBRT has been investigated by Liveringhouse et al[17] who did not observe any complete pathologic response in a phase 2 trial using 28.5 Gy given in 3 fractions of 9.5 Gy with an interfraction interval up to 48 hours and surgical tumor resection after 6 to 8 weeks. The ABLATIVE trial, investigating preoperative partial breast irradiation in low-risk breast cancer patients postulates a pathological complete response rate of 45% or more with a single treatment radiotherapy of 20 Gy to the tumor and 15 Gy to 2 cm surrounding the tumor which hopefully will allow to select patients who can be spared from additional surgery.[18] So far, SBRT has been investigated for adjuvant and for preoperative RT. Rahimi et al[19] at the Southwestern Medical Center investigated postoperative SBRT after wide local excision of the tumor, and dose escalation for early-stage breast cancer using doses up to 40 Gy in 5 fractions were tolerated well. Thus, today it remains unclear, which dose is mandatory for local disease control of early-stage breast cancer and feasible for definitive SBRT.

In the present planning study, we estimate the maximal tolerable dose for the delivery of a homogenous dose *in silico* using known dose constraints for potential toxicity to the tumor-surrounding tissue before testing definitive SBRT in a clinical setting. We choose a 5-fraction treatment schedule as this is a common and established fractionation schedule for SBRT of breast. As a secondary endpoint, the influence of the positioning on the maximum tolerated dose (MTD) was explored. Some of the results in the present work were posted on the medRxiv preprint server on April 27, 2020.

Methods and Materials

Patient eligibility and characteristics

A cohort of patients who underwent breast conserving surgery was admitted for postoperative RT. Planning computed tomography (CTs) scans were obtained in prone and supine position between January 2011 to January 2013 to introduce prone adjuvant RT into the routine for adjuvant RT. Selection criteria for this study were postmenopausal status, early-stage breast cancer (pT1-2 and pN0 or pN1a), and the availability of planning CT scans in supine and prone position. Patients provided informed consent to the reuse of their personal patient data in an anonymized manner for teaching and retrospective analysis. The ethical committee of the medical association of Saxony-Anhalt, Germany, approved communication of the data and publication of the study.

Study design, contouring of the organs-at-risk, and planning constraints

This study is a retrospective *in silico* cohort study. The sample size required for comparing an unpaired means in 2 population was calculated to be sufficient using 22 cases (https://link.springer.com/chapter/10.1007/978-981-16-5248-6_9). For each patient, planning CT scans were available in supine and prone position. The visible tumor bed (clinical target volume) with all the postsurgical clips and the postoperative seroma with an added margin of 2 cm resulted in the planning target volume (PTV). PTV margins were processed to remain ≥3 mm below the skin and not to overlap with the ribs. The contouring was performed by the treating physician (I.F.C.), using the ARIA Oncology Information System from Varian (Siemens Healthineers Company). The organs-at-risk (OAR) segmented were (1) fat tissue, (2) bones, (3) the left anterior descending artery, (4) skin, and (5) the left lung. The fat tissue was a spherical area from 5 to 15 mm surrounding the PTV avoiding any overlap with the skin and the thoracic cage, consisting of muscles and ribs. The skin was contoured over the entire irradiated breast and generated from the body contour subtracting 5 mm. All bones were outlined over the entire length and width of the PTV using the electron density segmentation using a threshold of 150 to 1500 Hounsfield units. The ipsilateral lung was reduced to a spherical area that overlapped with a working volume created from the PTV with an additional margin of 50 mm. As a surrogate for the dose delivered to the heart, the intraventricular artery (IVA) was segmented manually using a paint brush contouring tool with a diameter of 3 to 4 mm over the entire length of the left ventricle. The aim was to achieve the highest possible dose delivery without risk of damaging any organs. This MTD was calculated for potential OARs according to MP Guidelines/AAPM (American Association for Physics in Medicine) and the United Kingdom. Consensus statements on the normal tissue constraints for stereotactic ablative body radiation therapy.[14,15] The dose constraints used are applicable to hypofractionated RT given in

5 fractions, only and were for bone 1cc <35 Gy with a Dmax <43 Gy; for skin 10cc <36.5 Gy with a Dmax <39.5 Gy and 0.027cc <40 Gy. For fatty tissue, the dose was limited to 0.5cc <40 Gy if PTV was ≤124cc or 0.5cc to <37.5 Gy if PTV was >124cc. For the ipsilateral lung, the constraints were a maximum of 1500cc receiving <12.5 Gy and 1000cc <13.5 Gy. For the IVA 0.5cc was allowed to be given <18 Gy with a Dmax <20 Gy.

Radiation therapy planning

Plans in supine and prone position were generated with Eclipse, Acuros version 16.0 (Varian). The radiation fields were designed to cover the clinical target volume with a boost dose and in addition a larger volume surrounding the clinical target volume with residual radiation. The PTV was treated with a dose containing ≥95% of the prescribed dose, not exceeding 107% within the target volume. The starting dose was 6 Gy in 5 fractions with plans normalized to target mean dose, resulting in a total of 30 Gy. Dose escalation was stopped as soon as an OAR reached the MTD in supine and prone position. For both, supine and prone position, a hybrid planning technique was used, consisting of a 3-dimensional plan contributing roughly 40% of the dose and coplanar partial volumetric arcs to the same isocenter. A combination of dynamic arcs and static fields was used to optimize the dose fall-off and minimize the dose given to nontarget tissues surrounding the tumor.[20,21] The beam energies used were 6 MV in all patients. The geometry was coplanar (Fig. 1). The radiation geometry was chosen such that the field borders to the lung and the ribs were tangents. The 3-dimensional conformal plans avoided the contralateral breast completely, while keeping the distance between field entry and target volume as small as possible. Four fields were used, 2 static with dynamic wedges and 2 partial modulated arcs. The angle for the static fields in prone position was 280° to 325° and the opposing static field was kept stable at 176°. The arcs were delivered from 181° to 297°-337° clockwise and counterclockwise. In supine position, 2 static fields with wedges were used at an angle of 296° to 359° and the opposing static field from 107° to 145°. The partial arcs ranged from 292°-349° to 179°, except for medial tumors, the arcs ranged from 292°-349° to 106°-179°. During the optimization, the 3-dimensional conformal radiation plans were used as the dose-basis. The lung, heart, and contralateral breast were spared as far as possible. Finally, both plans were fused.

Study endpoints and statistics

The primary endpoint was to obtain clinically acceptable and feasible plans useful for treatment of patients with SBRT/partial breast irradiation before surgical removal of the tumor. The Wilcoxon signed-rank test was used to compare the MTD of an OAR in supine and prone position and to determine whether positioning was statistically significant. P values < .05 were defined to be statistically significant, meaning that positioning directly influenced the MTD of an OAR. We compared the MTD in supine and prone position using the χ^2 test. P values < .05 were defined to be statistically significant.

Results

Patients

Twenty-two postmenopausal patients with early-stage invasive ductal carcinoma subjected to dual RT planning in supine and prone position were identified and their planning CT scans were used for comparative SBRT planning. Apart from 2 patients with pT2, tumor stage did not exceed pT1c pN0/pN1a. Nine patients had Her-2 negative disease and 13 were Her-2 positive. Patients with left-sided disease were selected with the intention to use the optimal RT plan with lesser dose to the lungs and to the left descending coronary artery to minimize exposure to radiation in case of preexisting risk factors such as a smoking history, or a history of cardiovascular health conditions.

Assessment of maximum tolerated dose

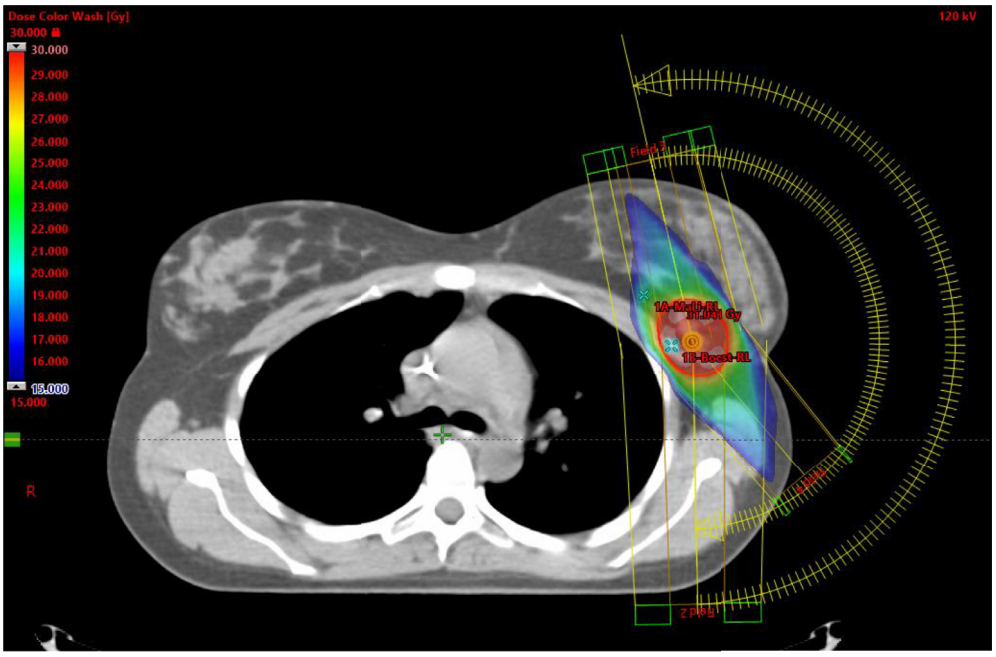
Results are summarized in Table 1. Target volumes (PTV) differed for the supine and the prone position. Overall, the MTD was comparable for patients in supine and prone position. In supine position, the mean maximal tolerated boost dose was 45.9 Gy (range, 38.8-53.9 Gy). Fifteen out of 22 patients reached MTDs in supine position (P = .02) than. In prone position the mean maximal tolerated boost dose was 46.1 Gy (range, 37.3-53.9 Gy). Seven out of 22 patients reached MTDs in prone position (Fig. 2). For a single fraction, the mean PTV in supine was a daily dose of 9.3 Gy (range, 6.2-15.6 Gy) and in prone 9.9 (range, 5.5-15.6 Gy) (P = .7).

The median total doses applicable in 5 fractions in supine and prone were comparable, supine 45.9 Gy (range, 45.2-46.6) and prone 46.1 Gy (range, 45.5-46.7) (P = .7), respectively. On average, slightly higher doses to the PTV were achievable in prone position than in supine position, although the highest dose achieved was observed in supine position (Fig. 3). A normal distribution was observed.

Limiting organs

Fat tissue was the most common dose limiting structure in supine position (11 of 22) and prone position (15

A



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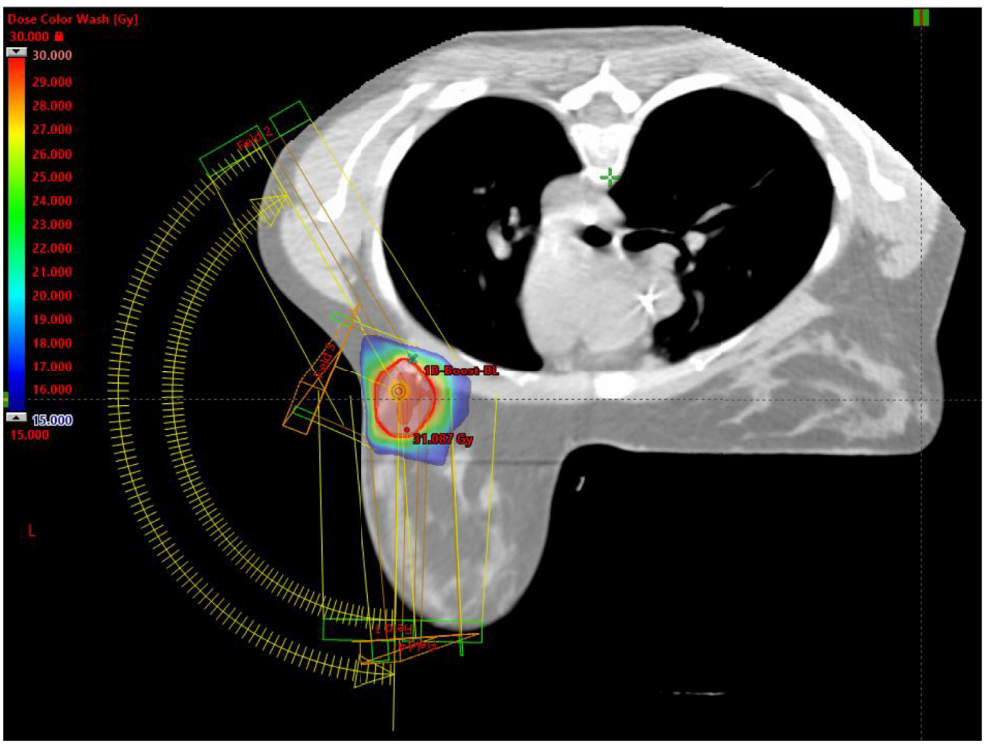

Figure 1 Beam geometry for stereotactic body radiation therapy. Two partial arcs used clockwise and counterclockwise complemented by 2 conformal fields with wedges. (A) Supine position. (B) Prone position.

Table 1 MTD over 5 fractions in supine and prone position

	Supine position		Prone position		
	Limiting organ (s)	MTD of limiting organ (Gy)	Limiting organ (p)	MTD of limiting organ (Gy)	Δ MTD supine and prone (Gy)(accepting supine position as baseline)
Patient 1	Bone	42.5	Fat	42.2	−0.3
Patient 2	Skin	46.0	Fat	41.5	−4.5
Patient 3	Skin	42.4	Skin	47.7	+5.3
Patient 4	Fat	47.3	Fat	42.2	−5.1
Patient 5	Bone	44.6	Fat	41.5	−3.1
Patient 6	Bone	47.9	Skin	47.7	−0.2
Patient 7	Skin	44.4	Skin	39.9	−4.5
Patient 8	Fat	48.2	Fat	50.6	+2.4
Patient 9	Skin	40.3	Skin	47.3	+7.0
Patient 10	Skin	38.8	Fat	47.4	+8.6
Patient 11	Fat	49.8	Fat	47.8	−2.0
Patient 12	Fat	51.4	Fat	50.0	−1.4
Patient 13	Skin	40.4	Skin	37.3	−3.1
Patient 14	Fat	48.6	Fat	47.7	−1.9
Patient 15	Fat	45.3	Fat	49.5	+4.2
Patient 16	Fat	47.6	Fat	43.4	−4.2
Patient 17	Fat	47.5	Fat	46.3	−1.1
Patient 18	Skin	40.5	Skin	46.0	+5.5
Patient 19	Fat	53.9	Fat	48.1	−5.8
Patient 20	Fat	42.7	Fat	42.1	−0.6
Patient 21	Bone	49.1	Bone	47.7	−1.4
Patient 22	Fat	44.3	Fat	43.0	−1.3
Sum average		45.9 (±3.9 SD; range, 38.8-53.9)		46.1 (±3.2 SD; range, 37.3-53.9)	

Abbreviation: MTD = maximum tolerated dose.

of 22). The maximal dose (Dmax) to the fat tissue was 40.0 Gy (±3.3 Gy) in supine and 40.0 Gy (±3.3 Gy) in prone position (P = .3) (Fig. 4A, B).

Bone was a dose-limiting organ in 4 of 22 patients in supine and in 1 of 22 in prone position. The maximal dose (Dmax) to the ribs was 31.4 Gy (±9.5 Gy) in supine and 21.4 Gy (±11.0 Gy) in prone position (P = .0001) (Fig. 4C, D). Changes in the distance between bone and tumor mass can be explained by gravity, decreasing the distance in supine position. For tumors located close to the thoracic wall, bone is more likely to be the limiting organ in supine compared with prone position.

Skin was limiting in supine in 7 of 22 patients and in 6 of 22 in prone position. The maximal dose (Dmax) to the skin was 30.5 Gy (±7.4 Gy) in supine and 31.0 Gy (±7.0 Gy) in prone position (P = 8) (Fig. 4E, F).

The maximal dose to *1000cc of the ipsilateral lung volume* was 0.34 Gy (±0.1 Gy) in supine and 0.29 Gy (±0.01 Gy) in prone position (P = .85). Dose application to *a portion of the heart* was monitored, however not considered for the calculation of the MTD.

The left anterior descending artery and the ipsilateral lung were never the limiting organ, independent of the body positioning. The maximal dose to the IVA was 12.2 Gy (±3.1 Gy) in supine and 35.1 Gy (±5.7 Gy) in prone position (P = .0004). Thus, a higher radiation dose to the coronaries is observed in prone compared with supine position.

In summary, in most cases the positioning was not crucial. Patients with tumors very close to the thoracic cage, prone positioning might increase the distance from the tumor to the thoracic cage and might be preferable. On the other hand, patients with cardiac

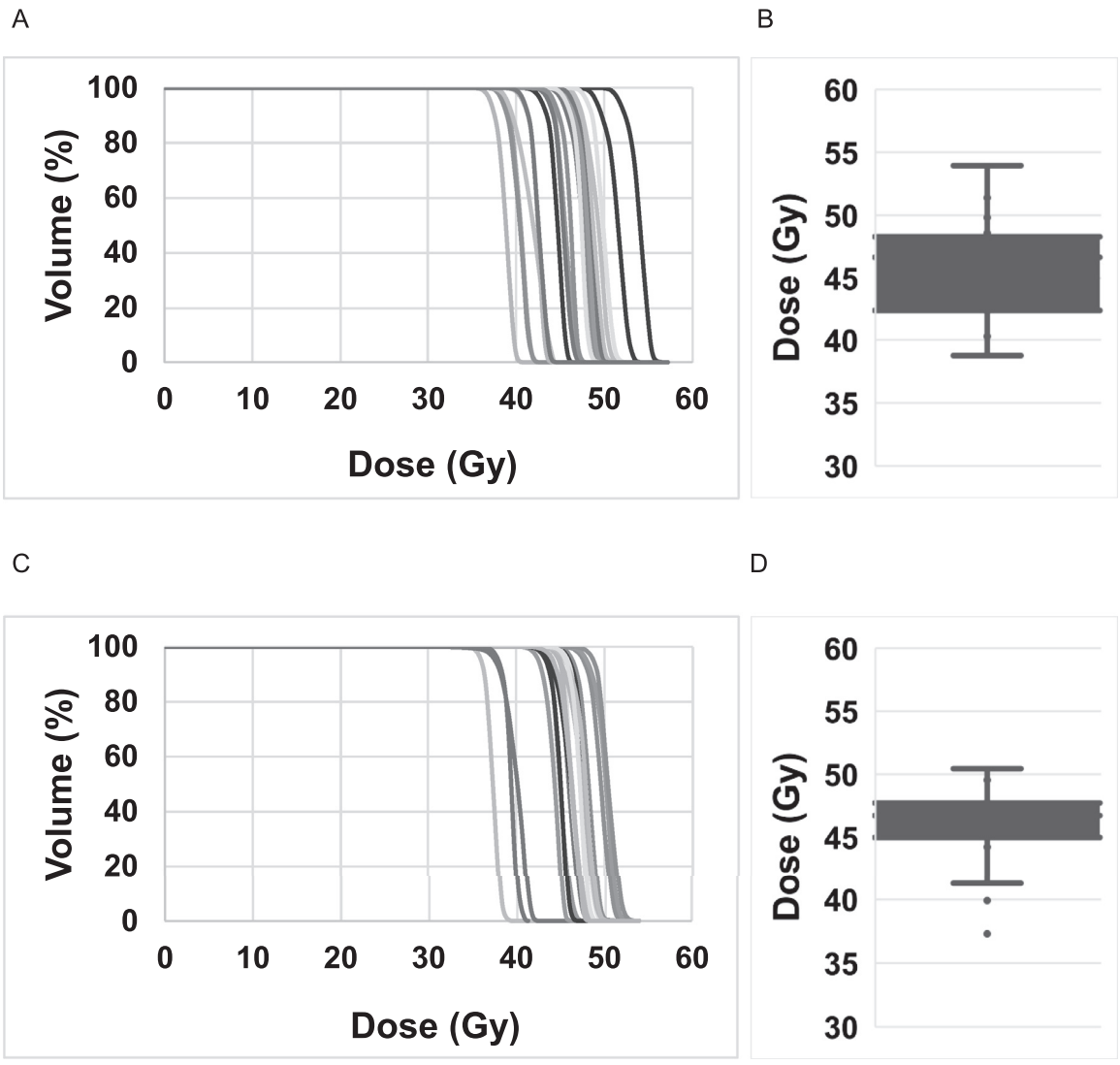

Figure 2 Target volume coverage as a function of maximum tolerated dose (MTD). (A) Summary of dose-volume histograms (DVHs) in supine position. (B) Box plot of MTD to planning target volume (PTV) in supine position. (C) Summary of DVHs in prone position. (D) Box plot of MTD to PTV in prone position.

risk factors are likely to receive a lower radiation dose to the IVA if positioned supine. Thus, a proper risk assessment according to individual medical characteristics is necessary before choosing the optimal positioning for a single patient.

Discussion

SBRT of early-stage breast cancer remains an experimental treatment and published data are scarce.[22] The current knowledge about the efficacy of SBRT relies on studies on preoperative partial breast irradiation followed by tumor resection, for example with 30 Gy in 5 fractions[23] or 40 Gy in 10 fractions[19,24] followed by consolidative surgery. The optimal and safe doses with high probability of sterilization of breast cancer cells has not been defined. Lischalk et al[25] suggested definitive therapy of early-stage breast cancer with 50 Gy delivered in 5 fractions using a homogenous dose to the target volume for protons and photons.

In the present series, we explored the MTD for SBRT to the target structure and observed a significant range of variability. We took advantage of a series of planning studies that were used to compare prone and supine position for patients undergoing postoperative RT of the left breast. The statistical characteristic of the cohort was favorable and the doses applicable revealed a normal distribution for prone and supine position. Thus, the numbers analyzed were sufficient to be conclusive on the possible dose for potential fat tissue necrosis or exceeding constraints of the ribs.

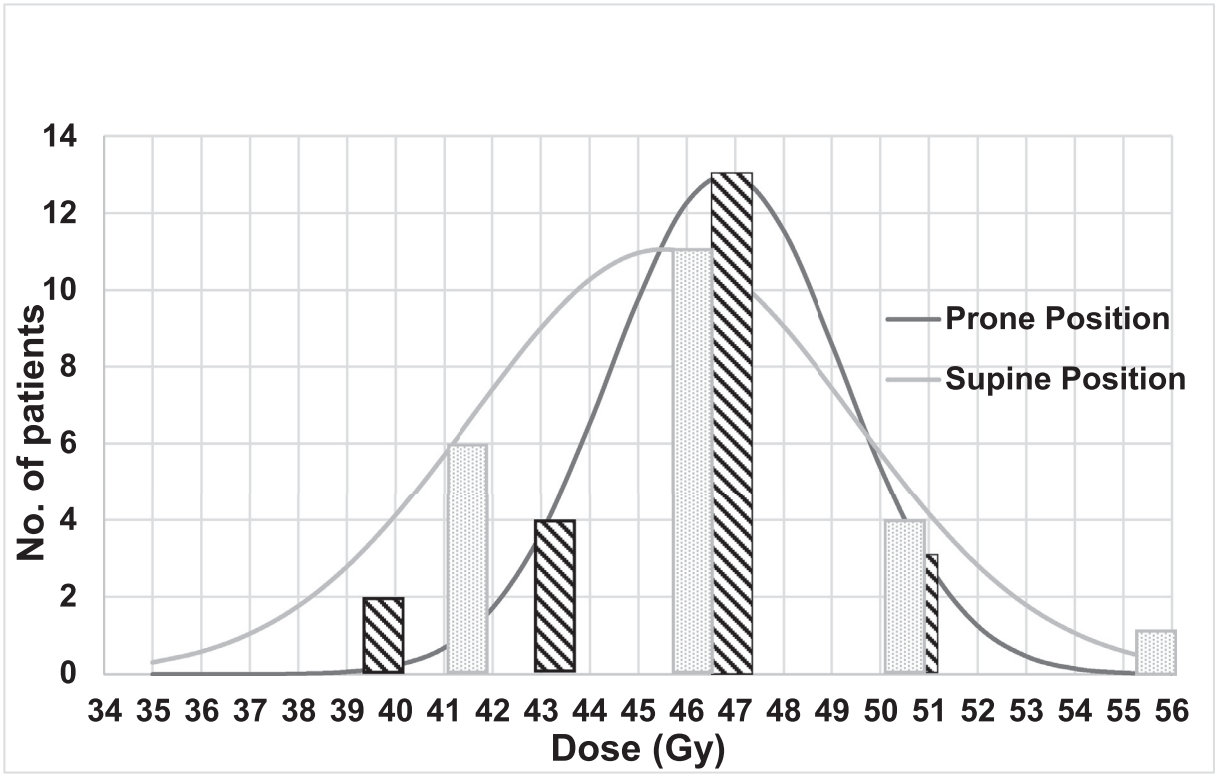

Figure 3 Normal dose distribution of maximum tolerated doses in supine and prone position.

We found that SBRT should be explored in a clinical setting at doses between 40 and 50 Gy if delivered within 5 consecutive days. Higher doses within the target volume while loosening the target dose uniformity constraint over 107% might be sensible in a subsequent clinical trial, especially if an integrated boost to a visible gross tumor volume can be applied while the exposure of the normal tissue remains limited to doses described as observed. In the present study, we used stringent dose constraints to avoid exceeding doses within the target volume to minimize the risk of fat tissue necrosis. Tight constraints of dose homogeneity enhance the comparability of treatment effects and treatment effects in a clinical trial in patients.

The predictive doses for safe definitive SBRT varied considerably. In most of the patients in our study, fat tissue was the limiting OAR to dose escalation, independent of body positioning, which concurs with previous observations. The larger fat tissue volume, the higher the risk of fat tissue necrosis. Rahimi et al[19] reported that fat necrosis is more likely to occur when the PTV is larger than 124 cm^3. However, fat necrosis represents a toxicity of a limited threat and rarely will lead to grade 4 toxicity. Thus, for a definitive nonsurgical approach, higher doses than reported by Rahimi et al[19] might be desirable. Furthermore, the use of higher energies than 6 MV to reduce dose to the fat tissue remains to be shown, although higher energies may deliver more dose to other thoracic organs.

In supine position the ribs became the limiting factor for dose escalation, especially for tumors located close to the thoracic wall. The risk of injury of the ribs can be reduced by positioning prone to pull the PTV away from the thoracic cage. Positioning preference should be evaluated individually. The statistically significant differences of the radiation doses given to the surrogate of the heart, the IVA, were clinically negligible in the present study.[19]

Several caveats apply to the present study as it is an explorative, preclinical, and small planning study. The suggested doses need to be confirmed in a prospective controlled clinical setting. We used only 1 fractionation schedule, and maybe a different schedule could be preferable. Our conclusions on the maximal doses rely on previously published toxicity data. Toxicities might occur at lower dose levels then we would except from this planning study. Furthermore, although tumors close to the thoracic wall may benefit from therapy in prone position, we can assume that other parameters, such as tumor size might mitigate the advantage of prone positioning. The case of high-grade nonmetastatic tumors remains to be defined for SBRT.

Taken together, to assess the efficacy of definitive RT in nonmetastatic breast cancer, aiming for the maximal doses for SBRT should be conclusively investigated in early-stage breast cancer. An approach using 2 dose levels in 5 fractions could be preferred in a clinical trial, such as treating the peri-tumoral tissue with low doses 37.5 Gy at the PTV margins and covering the macroscopic tumor

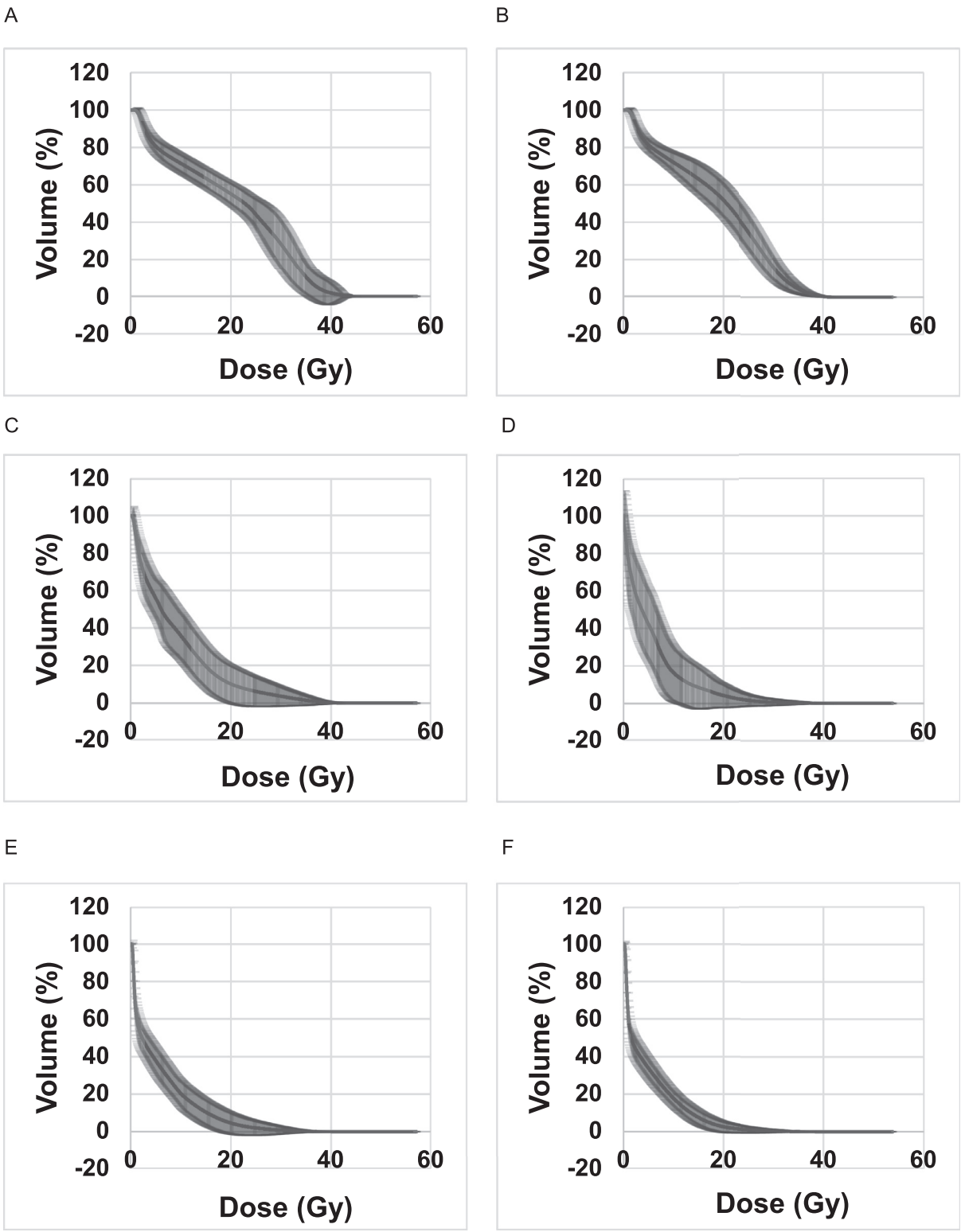

Figure 4 Doses to organs-at-risk. (A) Mean dose-volume histogram (DVH) of fat in supine position. (B) Mean DVH of fat in prone position. (C) Mean DVH of bone in supine position. (D) Mean DVH of bone in prone position. (E) Mean DVH of skin in supine position. (F) Mean DVH of skin in prone position.

with doses up to 50 Gy or higher, if dose escalation reveals to be feasible in a phase 1 study. This preclinical study allows us to initiate a clinical trial for SBRT as a curative therapy in early-stage breast cancer.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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