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RESEARCH PAPER

Dosimetric advantage of ipsilateral lung and cardiac sparing of left breast cancer prone position compared with supine free breathing in the COVID-19 era and personalized medicine

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ABSTRACT

Background: As coronavirus disease 19 (COVID-19) run unabated across the globe, its potential survival detrimental effects on lung function may be potentiated by systemic therapy and/or radiotherapy. Limiting lung exposure to high radiation dose in addition to sparing the heart may be critical for left-sided breast cancer patients. Deep inspiration breath-hold allows heart sparing. However, a minority of patients cannot hold breath for radiotherapy. We aim to evaluate whether a prone setup can be advantageous in these patients.

Materials and methods: Left breast cancer patients who had dual supine and prone planning, both in free-breathing, were retrospectively identified. A multiple-structures penalty score was computed from the mean absolute dose deviation (MADD) to heart, lungs, breasts, and tumor bed for each supine and prone plan. Dosimetric advantage of prone was assessed by the reduction of penalty score compared with supine. Patients' characteristics effect on the reduction of penalty was analyzed using robust linear regression.

Results: The prone *vs.* supine MADD for 27 patients demonstrated significant sparing for the ipsilateral lung and was 0.6 *vs.* 3 Gy, respectively, without differences regarding heart and target volumes. The average penalty ± standard deviation was 0.90 ± 0.28 Gy prone, *vs.* 1.13 ± 0.38 Gy supine, p = 0.024. Overall, 70.4% (19/27) patients had a reduction of penalty with prone setup, as compared with 29.6% (8/27) supine, p = 0.0065. Pre-dosimetry characteristics could not predict the reduction of penalty.

Conclusion: Prone conferred substantial lung sparing without dose-deterioration to other structures, providing a significant advantage as compared with supine free-breathing radiotherapy in left-breast cancer patients.

Keywords: dose-volume metric; quality planning audit; mean absolute dose deviation; penalty score; effective dose

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Introduction

Meta-analyses have established that adjuvant radiotherapy improves survival for breast cancer. The benefit can, however, be reduced by cardiovascular or other toxicities, most notably, with left breast cancer because of the increased radiation dose to the heart. Voluntary deep inspiration breath-hold (DiBH) is a highly efficient technique for reducing doses to the heart during radiotherapy, as demonstrated by educational materials on how to implement the technique [1, 2]. However, some patients, in particular older ones, may not be able to hold their breath for 20 seconds to allow breast irradiation due to co-existing heart and/or lung disease or altered mental status. In that case, another potential cardiac sparing technique which does not require breath hold is the prone breast irradiation. This positioning increases the distance of breast and the surgical cavity from the thoracic wall and might allow less lung and cardiac irradiation, even though the heart also shifts closer to the breast. As a caveat, the prone radiotherapy technique is more labor intensive, which has limited its application in clinical practice in the past. However, since the coronavirus-19 pandemic, many breast cancer patients are at risk of infection before, during, and after treatment [3]. The oncology landscape has also been changing. Most of those patients require systemic therapy which may or may not be combined with radiotherapy. Recent advances in biomarkers, and next generation sequencing (NGS) allows oncologists to personalize systemic treatment based on receptor status, genes mutation and program death ligands 1 expression (PD-L1) [4]. Tamoxifen, taxanes agents, HER-2 inhibitors, and immunotherapy with check point inhibitors have been associated with an increased rate of pneumonitis which may be indistinguishable from viral pneumonitis, and potentially worsened with breast radiotherapy [5, 6]. Preliminary studies also suggest an increased risk of death for breast cancer patients who were exposed to previous lung irradiation when they became infected with the coronavirus. As the pandemic continued unabated due to the emergence of new strains, a question arose whether radiation therapy techniques need to be optimized to minimize lung irradiation, and the potential risk of severe pneumonitis if the patients become infected during their disease course, prompting to conduct the following study. We would like to evaluate the dosimetric impact of prone versus supine free-breathing breast radiotherapy for women with left breast cancer who could not undergo treatment in a breath-hold condition to assess whether prone improves lung and/or heart sparing without deteriorating the dose distribution to other organs and targets, as compared with supine. A secondary objective is to search for factors that predict whether prone or supine setup will result in a dosimetric advantage.

Materials and methods

This Institutional Review Board-approved and ClinicalTrials-registered study retrospectively selected patients who had undergone breast conserving surgery for primary left breast cancer, were referred for adjuvant radiotherapy between September 2010 and August 2013, gave written informed consent and underwent computed tomography (CT) simulation and treatment planning in both prone and supine positions in free breathing. The patients were positioned supine on an inclined breast board with arms extended above the head and prone using the Bionix Prone Breast System in 2010–2012 and the Varian Pivotal Prone Breast Care in 2013. CT images were acquired with the same parameters in both positions. The right (contralateral) breast rested on a 5-degree foam wedge. The left (ipsilateral) breast was inspected to hang unhindered and centered through an opening in the couch support. Prone CT-images were acquired with the same parameters as supine. For treatment planning, the breast clinical target volume (CTV) and tumor bed CTV were delineated, and planning target volume (PTV) equated CTV without expansion [7]. The prescribed dose in most patients was 47.25 Gy in 21 fractions, 4 fractions/week. Treatment planning used tangential fields without boost using Varian Eclipse. Constraints were 95% of the prescribed dose covering 95% of breast PTV and 100% of tumor bed PTV, breast PTV V107% < 2 cc, ipsilateral lung V20 Gy < 10%, heart near max D2% < 15 Gy, and heart mean dose < 3 Gy. The beams avoided the contralateral breast. Forward intensity modulated radiotherapy was applied using combination of wedges, field in field compensation and mix of different photon energies as needed to meet constraints. The chest wall was excluded from the breast

PTV. The maximum lung distance allowed was 2 cm. Heart shielding was systematic if the heart appeared in the fields using a multileaf collimator. The doses were proportionally converted to a nominal prescription of 42 Gy.

We used a penalty score to evaluate the overall dosimetric impact of treatment plans. The penalty score was computed as a weighted average of the mean absolute dose deviations (MADD) to organs and target structures, as detailed in Supplementary File. Briefly, the MADD measures how far the doses to an organ exceed zero (in an ideal plan, the doses to organs at risk should be zero) and how far the doses to a target deviate from the prescribed dose (in an ideal plan, the doses to a target should be exactly the prescription, not more, not less). The penalty score summarizes how far a plan under evaluation deviates from the ideal of delivering zero dose to organs and exactly the prescribed dose to targets. The penalty score is expressed in the same units as the dose prescription. A zero score indicates a perfect plan. There is no upper bound. The change in penalty score was assessed by the counts of patients who benefitted from prone and by visual summarizing displays. Robust linear regression [8] and fractional polynomial regression [9] were used to evaluate potential predictors of the dosimetric gain: patient's age, height, weight, body mass index (BMI), tumor location, planning breast volume, patient's preference, CT measurements of the breast depth supine and prone (distance from the breast surface to the pleura as defined in [10]), and post-dosimetry penalty scores. The present study data differ but the methods are identical to those applied in the two previous studies [7,10].

Pairwise comparison of continuous variables used the Welch t test assuming unequal variances, and comparison of categorized tabular data used the chi square test with continuity correction for proportions [11]. Statistical computations used R version 4.1.2 [12]. Visual display used the package *ggplot* [13]. Regression analyses used *MASS* [8] and *mfp* [9].

Results

From an original list of 299 dual prone-supine breast CT-simulations, 296 were evaluable dual CT-plans, of which a total of 145 left breast treatment plans were available for analyses [10]. After exclusion of repeat CT (2 patients) and exclusion of cases where supine CT was in deep inspiration breath-hold (116 patients), there remained a total of 27 patients with dual prone and supine free breathing CT, representing the study population.

Two patients had bilateral breast cancer; the left breast radiotherapy plans were done separately from the right breast planning. Ten patients (37.0%) were prescribed with 42.56 Gy to the breast in 16 fractions, 5/week [14], seventeen (63.0%) with 47.25 Gy to the breast in 21 fractions, 4/week . These doses were proportionally converted to a nominal ipsilateral breast prescription of 42 Gy. Most patients were aged ≥ 65 years, with a distribution comparable to Swiss registry data (Tab. 1). Body mass index overweight and obesity represented 29.2 % of the non-missing records. Lymph nodes were involved in 28% of the patients, but nodal irradiation was not retained because of a low-risk lymph node ratio or concern for shoulder-arm morbidity in one patient with a higher risk lymph node ratio [15]. Patient's preference was supine in 55.6% of those who responded to the query, while 44.4% preferred prone or had no preference.

The pooled DVHs comparing prone and supine plans — graphically enhanced by using a square root transform to zoom into the lower doses — displayed indistinguishable dose-volume patterns regarding the ipsilateral breast, the heart, the tumor bed, and the contralateral lung (Fig. 1). The contralateral breast received more dose prone than supine, but most of the DVH curve was well below 1 Gy. The ipsilateral lung received markedly more dose from supine than from prone radiotherapy. The MADDs confirmed the visual display, with no meaningful differences of the MADDs regarding the heart, the contralateral lung (statistically reaching significance due to narrow spread of the standard deviations), the ipsilateral breast and the tumor bed (Tab. 2). The median MADD to the contralateral breast was 0.6 Gy prone *vs*. 0.2 Gy supine. The median MADD to the ipsilateral lung was 0.6 Gy prone, *vs*. 3.0 Gy supine, i.e. a fivefold reduction of the dose. The boxplot of the MADDs — also enhanced by a square root zoom into the lower doses — revealed the same information, namely a small increase of dose to the contralateral breast with prone, in contrast with a marked increase of dose to the ipsilateral lung with supine,

Table 1. Patient's characteristics

Characteristic	N (%)
Total	27
Age [years]	
< 50	4 (14.8%)
50, < 65	8 (29.6%)
≥ 65	15 (55.6%)
Weight [kg]	
Missing	1
< 60	3 (11.5%)
60, < 70	12 (46.2%)
70, <80	6 (23.1%)
80, < 90	2 (7.7%)
≥ 90	3 (11.5%)
Body mass index [kg/m^2]	
Missing	1
< 25	11 (42.3%)
25, < 30	10 (38.5%)
30, < 35	3 (11.5%)
≥ 35	2 (7.7%)
Left breast volume [mL]	
< 200	1 (3.7%)
200, < 400	3 (11.1%)
400, < 600	13 (48.1%)
600, < 800	6 (22.2%)
800, < 1000	2 (7.4%)
≥ 1000	2 (7.4%)
Tumor location	
Lower inner	1 (3.7%)
Central	3 (11.1%)
Upper inner	3 (11.1%)
Upper outer	13 (48.1%)
Lower outer	1 (3.7%)
Other	6 (22.2%)
Pathological stage	
0	3 (11.1%)
I	10 (37.0%)
II	14 (51.9%)
pT	
Tis	2 (7.4%)
T0	1 (3.7%)
T1	15 (55.6%)
T2	9 (33.3%)
T3	0 (0.0%)
Lymph node ratio	
Missing	2
0	18 (72.0%)
> 0, 0.20	6 (24.0%)
> 0.20, 0.65	1 (4.0%)
> 0.65	0 (0.0%)
Couch type	
Bionix	24 (88.9%)
Varian	3 (11.1%)
Patient's preference	
Missing	9
Supine	10 (55.6%)
No preference	6 (33.3%)
Prone	2 (11.1%)
Treatment applied	
Supine	6 (22.2%)
Prone	21 (77.8%)

but there were no remarkable difference regarding the four other structures (Fig. 2).

Overall, the penalty score was reduced from 1.13 Gy (standard deviation ± 0.38) supine, to 0.90 Gy (± 0.28) prone, $p = 0.024$. Out of the 27 patients who were DiBH-unable, 19 (= 70.4%) had a reduction of penalty with prone setup, as compared with 8 patients (= 29.6%) who did not benefit from the prone setup (Fig. 3), $p = 0.0065$.

None of the pre-dosimetric characteristics could reliably predict a setup advantage with prone or supine (Tab. 3). The regression coefficient of lungs volume lost significance when the single outlier shown in the scatter plot was removed (Supplementary File — Fig. S1). In contrast to the pre-dosimetry characteristics, the post-dosimetry penalty scores were significant predictors of a gain to switch from a setup to another. Table 3 suggests a scenario where a patient had only a supine plan, she could benefit from switching to prone if her penalty score supine was > 1 Gy, and conversely if a patient underwent only a prone simulation, she could benefit from switching to supine if her penalty score prone was > 1.1 Gy.

Discussion

DiBH-inability

Inspiration breath-hold is advantageous for the heart and lungs in the radiotherapy of left breast

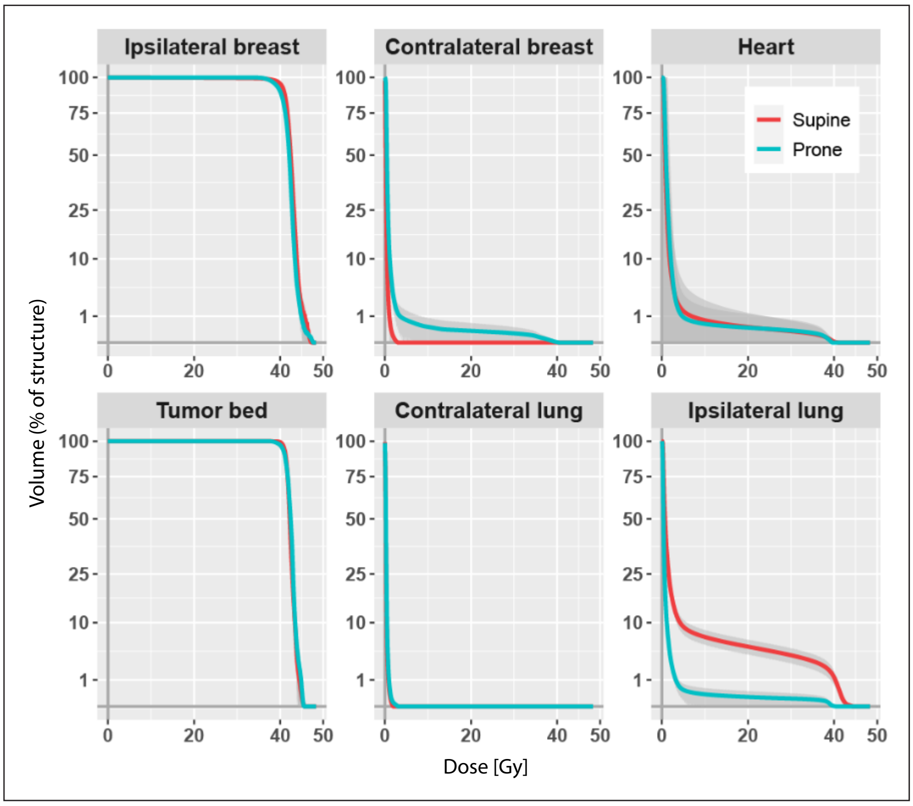

Figure 1. Averaged cumulative dose-volume histograms by structure and setup for a prescription of 42 Gy to the ipsilateral breast. Volume, square root scale. Dark grey, 99% confidence band

Table 2. Mean absolute dose deviation (MADD) by structure and setup

Structure	MADD Supine [Gy] Median (range)	MADD Prone [Gy] Median (range)
Heart	1.1 (0.5, 2.8)	1.1 (0.8, 3.3)
Contralateral lung	0.2 (0.1, 0.4)	0.3 (0.2, 0.3)
Ipsilateral lung	3.0 (0.7, 8.0)	0.6 (0.3, 1.8)
Contralateral breast	0.2 (0.0, 0.6)	0.6 (0.2, 3.1)
Ipsilateral breast	1.1 (0.7, 2.1)	1.0 (0.8, 1.8)
Tumor bed	0.6 (0.2, 1.6)	0.8 (0.3, 1.9)

cancer, but without an apparatus a small proportion of patients cannot hold breath for the 20 seconds required to implement the technique. The percentage of breath-hold unable patients (27 out of 145) was 18.6%, which is consistent with other observations. DiBH inability has been reported to be about 20% (26/130) [16], 14% (20/144) [17], 21% (56/272) [18] or 15% (41/280) [19]. DiBH is not a solution for every case [20], and in addition to this, one in five or one in six patients cannot even undergo DiBH. Intriguingly, the dosimetric outcome of these DiBH-unable patients has not received much attention, even though they are in no less need of heart sparing than DiBH-able patients. In addition, among older patients with mental impairments, following instruction to hold the breath may be a challenge. In fact, breath holding has been used as a marker to assess individual mental decline with age [21]. Thus, this technique may not be suitable for older cancer patients with multiple co-morbidities who may benefit the most from cardiac and lung sparing.

Of note, there were no differences regarding the doses to the heart. This might be explained by heart shielding that was applied in the treatment planning for supine and also for prone setup.

Population dosimetric gain

We analyzed and presented the results as if the patients were in separate groups, while in fact, all underwent dual planning. Both options were open to each patient, and there was no restriction on choosing the plan perceived as most appropriate. Actually, 21 of the 27 patients were treated prone, and the other 6 were treated supine (Ta. 1). The "as-treated" average penalty score of

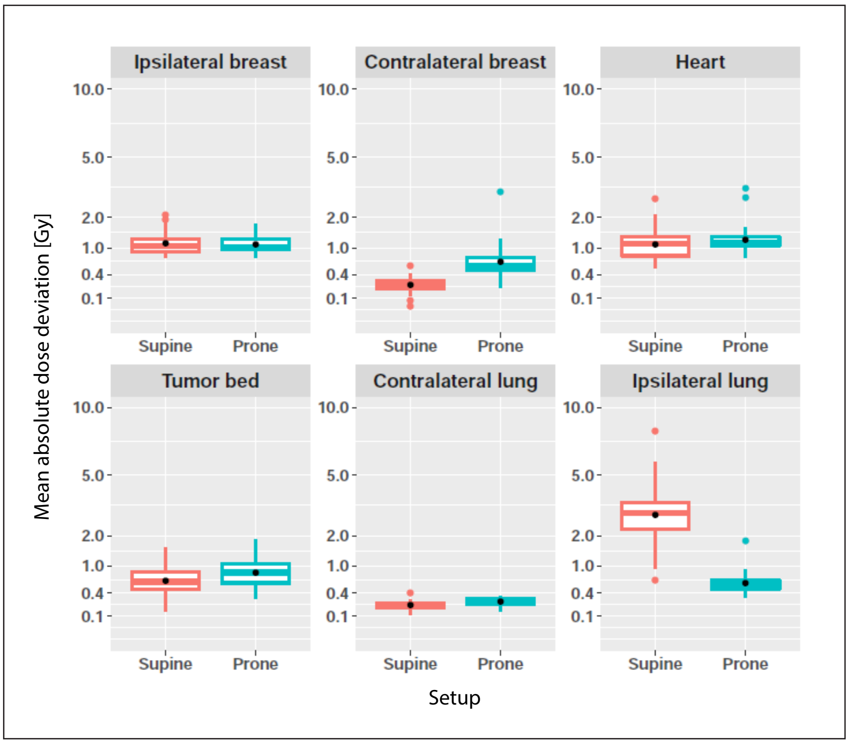

Figure 2. Mean absolute dose deviation (MADD) by structure and setup. MADD axis: square root scale. Box: lower quartile, median, upper quartile. Whiskers: 1.5 × interquartile range. Black dot: average of the MADDs. Color dots: outliers

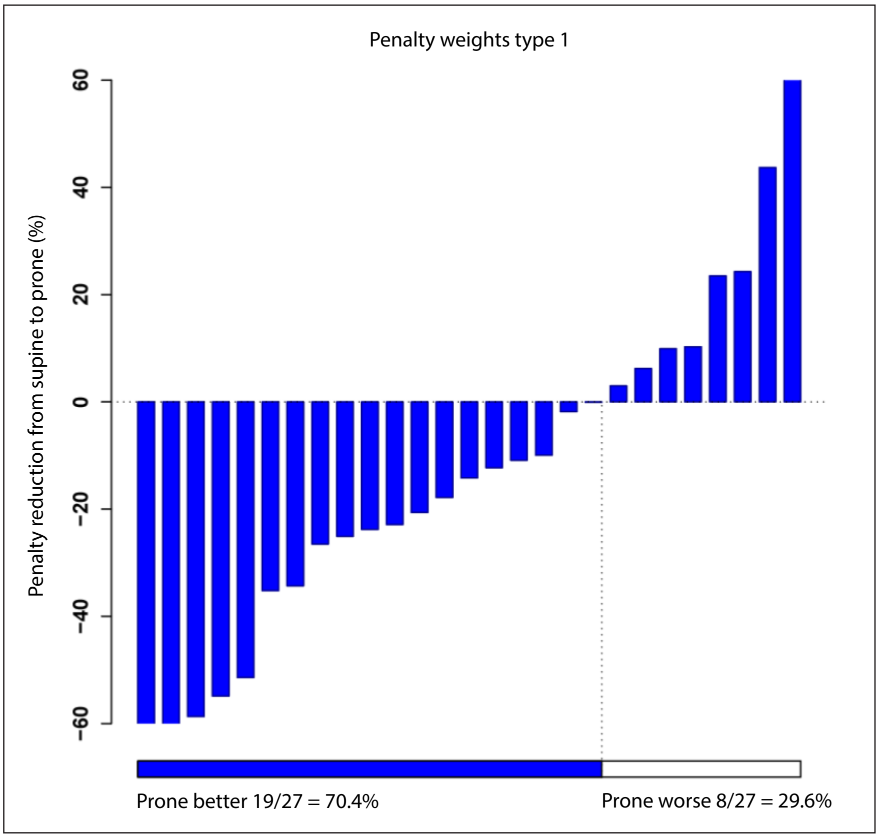

Figure 3. Waterfall plot of penalty change from supine to prone

Table 3. Robust linear regression predictors of a prone or supine advantage. A negative coefficient indicates further improvement of prone dosimetric advantage (reduction of penalty) when the characteristic increases. A near null coefficient or a ratio of coefficient over its standard error < 2 indicate that the characteristic is unlikely to affect the prone reduction of penalty

Characteristic	Intercept	Coefficient	Standard Error	Unit
PRE-DOSIMETRY				
Plasticity (pendulousness)				
Ratio breast depth prone/supine	–0.074	–0.050	0.435	Ratio
Breast depth difference prone–supine	–0.126	–0.006	0.051	Cm
Breast depth prone	–0.186	0.002	0.023	Cm
Breast/Body				
Breast volume/Body weight Ratio	–0.035	–0.014	0.023	mL/kg
Tumor location				
Lower inner quadrant (LIQ) *vs.* else	–0.199	0.421	0.387	Binary
Breast size				
Left breast volume supine	–0.117	–0.088	0.225	L
Right breast volume supine	–0.209	0.033	0.164	L
Left breast depth supine	–0.240	0.012	0.033	Cm
Inspiration breath-hold capability				
Left lung volume supine	–0.824	0.591	0.257	L
Total lung volume supine	–0.924	0.307	0.118	L
Right lung volume supine	–0.854	0.510	0.225	L
Age	0.487	–0.011	0.006	Years
Left anterior descending coronary-chest wall distance	–0.280	0.067	0.131	Cm
Body size				
Weight	–0.221	0.001	0.007	Kg
Body mass index	–0.155	–0.001	0.018	Kg/m^2
Heart volume supine	–0.292	0.217	0.669	L
Height	–0.975	0.495	1.149	m
Other				
Couch type Varian *vs.* Bionix	–0.126	–0.231	0.186	Binary
Preference prone *vs.* else	–0.220	–0.338	0.260	Binary
POST-DOSIMETRY				
Penalty prone	–1.118	1.048	0.178	Gy
Penalty supine	0.870	–1.006	0.114	Gy

the study population — whose final setup was necessarily blinded to scoring, which had not yet been developed at the time — was 0.88 Gy (SD 0.18, median 0.86, range 0.48–1.29). These scores are quite close to the theoretical best average penalty score of 0.84 Gy (SD 0.16, median 0.86, range 0.48–1.12) if the setup with the lowest penalty had been systematically selected. Without the option of a prone setup, all DiBH-unable patients would have been treated supine in free breathing, and they would have incurred a significantly higher 1.13 Gy penalty with scores as high as 2.53 Gy, an excess of up to 6% inadequate doses for a prescription dose of 42 Gy.

Comparative counts of patients

Discounting the magnitude of the penalty reduction, prone was advantageous in 70.4% (19/27) of the present DiBH-unable patients (Fig. 4). That percentage is intermediate between the right breast study that reported a benefit of prone in 81.5% (119/146) of patients [7], and the left breast study of DiBH-able patients that found a benefit of prone in 62.1% (72/116) of patients [10]. Simply put,

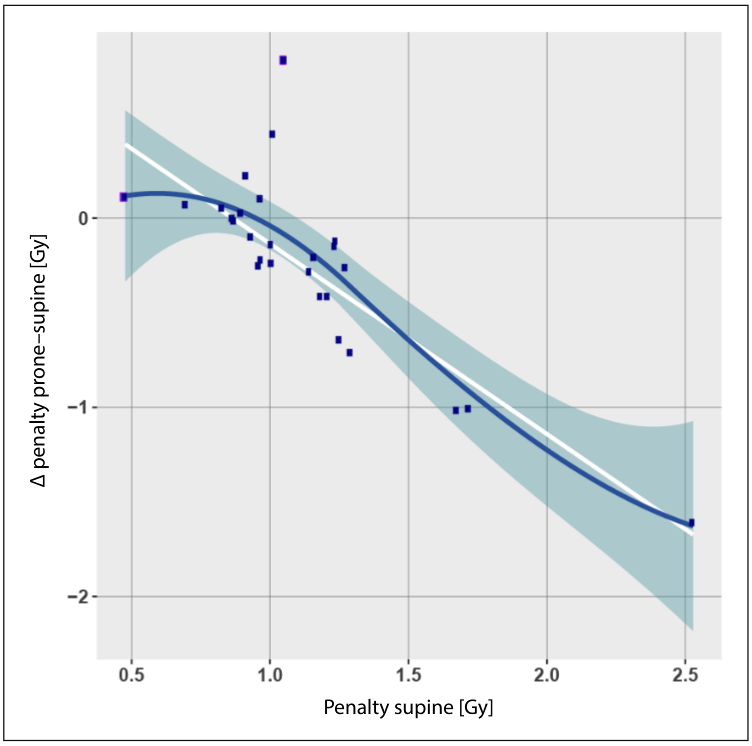

Figure 4. Δ Penalty (= penalty prone – penalty supine) as a function of the penalty supine. Blue curve, local polynomial fit; light blue band, 95% confidence. White line, robust linear regression

left breast cancer patients who were DiBH-unable gained more benefit from switching to prone than left breast cancer patients who were DiBH-able, though not as much as compared with right breast cancer patients, probably because of a larger area of the heart in contact with the chest wall in prone position.

Potential benefits in the landscape of personalized systemic treatment

Arguably some of the penalty reductions were quite small. There was less than a 20% change in penalty score in 11 patients when switching from one setup to the other (Fig. 3). The doses to organs at risk were low regardless of setup (Tab. 2). Most changes in penalty were less than 0.5 Gy (Fig. 4). But, to the individual patient, even 0.5 Gy might matter. More importantly in the era of COVID-19 and personalized systemic treatment, it may have a potential impact to minimize lung damage after breast cancer treatment. Most systemic therapies carry a risk of pneumonitis which may be significant depending on the agents used and may be exacerbated if combined with radiotherapy. As an illustration, the risk of pneumonitis was 14.6% and 1.1% for breast cancer patients receiving taxol-based chemotherapy and non-taxol based chemotherapy, respectively. If radiotherapy was also added to chemotherapy, the risk of pneumonitis significantly increased. The pneumonitis rate was 1.1% and 15.4% for radiotherapy alone and chemotherapy and radiotherapy, respectively [22]. A pooled analysis of 1150 cancer patients receiving trastuzumab reported a 15.4% of pneumonitis within the first 12 months of treatment. Even though most complications were low grade, it may have impact on patient quality of life [23]. More recently, immunotherapy with check point inhibitors has been reported to be effective for triple negative breast cancer. More breast cancer patients will receive immunochemotherapy and radiotherapy in the future due to its survival improvement [24]. Immunotherapy alone can cause pneumonitis. Thus, its combination with chemotherapy and radiotherapy may significantly increase the risk of pneumonitis. In breast cancer patients undergoing immunotherapy, grade 3-5 pneumonitis was 1.1% and 0% for chemotherapy and immunotherapy, and chemotherapy alone. respectively [25]. Even low dose radiation may contribute to lung damage for patients who had cancer and contracted COVID-19 infection. In a study of 107 patients who were infected and had prior lung irradiation for cancer, the mortality rate was significantly increased with the dose of radiation. Mortality rate was 30%, 35%, and 40% for 0 Gy, 2Gy, and 4 Gy, respectively, 14 days after hospital discharge [26]. Mean lung radiation dose was 0.2 Gy for the whole group. In a report of 123 breast cancer women who received breast cancer irradiation for early-stage disease, non-cancer death increased significantly during COVID-19 mortality and linked to a significant decline in heart and lung function [27]. As the viral infection continued unabated across the world, it seems prudent for clinicians to minimize lung irradiation, especially for older breast cancer patients, who are at higher risk of death if infected. The benefit of investing in prone radiotherapy equipment may be offset by the cost of pneumonitis care. It has been reported that patients who developed radiation-induced pneumonitis had frequent emergency room visits and had more hospital admission resulting in increased health care cost compared to those who did not [28].

Other penalty types

The penalty score of "type 1" is best suited for low-risk breast cancer, but for cases with adverse characteristics, such as negative hormone receptors, lympho-vascular invasion, or surgery with narrow margins, tumor control should be prioritized. In such cases, different weights would yield different penalty scores. The study was reconducted using weights according to various scenarios of high cardiac risk, high pulmonary risk, breast cancer risk, or secondary tumors (Supplementary File — Tab. S1). Prone positioning was beneficial in most scenarios, with varying percentages of patients benefiting depending on the scenario, 51.9% patients at high cardiac risk, 100.0% at high pulmonary risk, 48.1% at high breast cancer risk, and 77.8% at high secondary cancer risk (Supplementary File — Fig. S2). Overall, these percentages highlight the importance of considering different penalty types and weights depending on the specific characteristics of the patient and their condition.

Limitations

With only 27 patients, the chances of identifying significant predictive factors are limited. Breast volume, breast depth and breast plasticity could not be validated as predictors of a setup dosimetric gain [7,10]. We did not establish clear cutoffs for the minimum acceptable treatment plan, nor did we specify how much effort should be devoted to reducing the allowable dose deviations (MADD) and penalty scores. Additionally, because our study was retrospective, there may be recollection and data analysis biases. We also did not conduct dual-simulation for approximately 10–15% of eligible patients, and we did not record the reasons for this omission. The final contours were approved without blind assessment, and our study did not review the 3-dimensional dose distributions that determined the actual treatment given to patients.

Strengths

The same analytical methods used in other prone studies were strictly applied without altering any parameters. The data, which has been made available, is an important addition to the growing body of external datasets [20]. The strengths of our study are consistent with those of previous research. All treatment plans were done prospectively with the aim of delivering the best possible plan, regardless of patient position. As evidenced by the overall low doses to organs at risk, no attempts were made to adjust the plans in any way. Dual-planning ensured that each patient was treated as her own comparator, independent of other patients. Additionally, no patients were excluded from the analysis after the fact. Overall, our data provides a realistic insight into the potential benefits of prone setup for left breast patients who are unable to undergo deep inspiration breath hold.

Conclusion

In left breast cancer patients who could not hold their breath for deep inspiration radiotherapy, prone positioning increased slightly the dose to the contralateral breast, provided comparable doses to the heart, the ipsilateral breast, the tumor target volume, and the contralateral lung, and provided a fivefold reduction of the dose to the ipsilateral lung. This translated into a significant overall dosimetric advantage, which would be important with the increasing need to minimize lung damage.

Study registration

ClinicalTrials.gov NCT02237469, HUGProne, September 11, 2014, retrospectively registered.

Ethics approval

The study received approval at the Geneva University Hospitals Institutional Review Board.

Consent to participate

Patients signed informed consent to the radiotherapy procedures.

Consent for publication

Not applicable.

Availability of data and material

Data are available on Mendeley, https://dx.doi.org/10.17632/rv7pjnfhxx.1 .

Code availability

The study used free software available on https://cran.r-project.org/ .

Author contributions

V.V.H., N.P.N. and G.D. conceived the project; all authors performed the literature search and contributed to the literature analysis and synthesis of data; OG created the figures and tables; V.V.H. and N.P.N. wrote the article; and all authors were involved in further editing and finalising the manuscript.

Conflict of interest

V.V.H. and N.P.N. declare holding a patent for the calibration of radiation therapy treatment plans with a mean absolute dose deviation machine, US10668301B2.

V.V.H. initiated an agreement with Varian Medical Systems for the installation of the Varian Pivotal Prone Breast Care at the Radiation Oncology department of the Geneva University Hospitals, Geneva, Switzerland. V.V.H. declares 0.018% stock ownership in Affluent Medical, unrelated to the study.

M.K. declares receiving payment for a presentation on skin cancer by Sanofi — Pierre Fabre.

Giovanna Dipasquale declares to have a patent pending with Geneva University Hospitals (WO2020099510A2), planned on RT and Hyperthermia, and declares stock/stock options relationship with HeroSupport SA.

R.M.. declares stock/stock options relationship with TERAPET SA.

Other authors declare no conflict of interest.

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