

Review

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Review

The Prone Position Whole Breast Irradiation Paradox: Where Do We Stand? A Comprehensive Review

Chris Monten ¹, Wilfred De Neve ¹, Iliara Benevento ², Antonietta Montagna ², Edy Ippolito ³, Paola Anselmo ⁴, Luciana Rago ², Barbara D'Andrea ², Angela Solazzo ², Antonella Bianculli ⁵, Raffaele Tucciariello ⁵, Giammaria Fiorentini ⁶, Vito Metallo ², Simone Salvago ², Carmen Santoro ², Anna Vallario ² and Grazia Lazzari ^{2,*}

¹ Radiation Oncology Unit; GHENT University, GHENT, Belgium

² Radiation Oncology Unit; IRCCS -CROB, Rionero in Vulture (PZ), Italy

³ Radiation Oncology Unit; Campus Biomedico, Roma, Italy

⁴ Radiation Oncology Unit; Ospedale S. Maria, Terni, Italy

⁵ Physic Unit; IRCCS -CROB, Rionero in Vulture (PZ), Italy

⁶ Department of Oncology, San Salvatore Hospital, 61121 Pesaro, Italy

* Correspondence: grazia.lazzari@crob.it

Abstract

In the past two decades, the interest in prone position whole breast irradiation (WBI) as an effective and practical alternative to supine treatment has been growing a lot. Although solid scientific evidence have provided data of substantial dosimetric benefit and decreased toxicity, there is still a paradox in the radiotherapy community to adopt prone position WBI as valid alternative to supine radiotherapy (RT) in routinary clinical practice. A large number of prone trials have been conducted to assess and address concerns related to treatment in large and pendulous breasts and in left and right BC, nodal irradiation, and its reproducibility with Deep Inspiration Breath Hold (DIBH) delivery with photons or protons. Appropriate atlases have been defined to improve prone nodal irradiation. Additionally, more comfortable customised immobilisation couches have been constructed to permit IMRT beams arrangements. A search in literature databases with the keywords 'prone positioning radiotherapy', 'prone set up', 'prone breast radiation', 'prone breast and lymph node irradiation', 'prone position versus supine position', and 'prone DIBH' revealed a growing body of evidence from the past two decades. However, prone WBI is still underused. Given the paradox of advances and benefits of this positioning and the lack of drive in the radiotherapy community for its clinical implementation, the aim of this paper is to provide a comprehensive summary of innovations in this field to overcome this paradox and implement prone positioning in real life breast cancer radiotherapy.

Keywords: breast cancer; IMRT; DIBH; whole breast irradiation; photons

1. Introduction

Breast cancer (BC) adjuvant strategies encompassing advanced postoperative radiation modalities in conjunction with preoperative or postoperative novel systemic therapy have significantly enhanced the long-term survival prospects of BC patients and improved patients' long-term quality of life while attempting to minimise the radiation-induced side effects [1,2]. The vast majority of patients worldwide receive adjuvant radiotherapy for breast cancer in supine position although it could be challenging for patients with BC showing post-surgery discomfort in terms of arms pain or arthritic arm limitations. For example, scoliosis in older women hinders the alignment of the chest on the couch with the arm positioned above the head. Several criticisms concerning the irradiation of large and pendulous breasts in obese women because of the inflammation of the inframammary fold and axilla owing to hot spot deposition need to be considered [3]. In addition,

concerns to reduce the dose to organs at risk (OARs) such as the heart [4], left anterior descending coronary artery (LADCA), and ipsilateral of lung (IL) have impelled teams of radiation oncologists to search for practical solutions such as the use of deep inspiration breath hold (DIBH) modality for left-sided BC [5] while alternative treatment positions in prone or lateral decubitus [6,7] have been also investigated. Prone positioning has been the most studied modality since the first decade of 2000 and now it is under study in accelerated partial breast irradiation (APBI) use [8]. Prone positioning has been hypothesised a reasonable solution to treat pendulous breasts and reduce the dose to cardiac structures in left-sided BC since remote times [9]. Differences in prone dive and prone crawl have also been addressed as valid alternatives to the supine position in WBI, showing in both ways largest advantages for lung structures [10]. Nevertheless, there is still a paradox with solid scientific evidence of decreased toxicity on the one hand and lack of drive in the radiotherapy community for clinical implementation on the other hand. The purpose of this paper is to solve this paradox, encompassing a broad spectrum of prone positioning-related topics. It provides readers with effective insights into all the novel techniques and guidelines supporting this new approach as a good option in WBI. No automation tool was used during the literature search.

Real World Data Distribution of Prone WBI

Implementation of prone positioning is widespread but its use in routinary clinical practice is scarce with a patchy distribution. In Geneva University Hospitals this positioning has been introduced in the routinary clinical practice since 2010-2013 [11]; by a Spanish survey, prone position has been rarely adopted in only 3 of 40 centers [12]. In German-speaking countries, 1 (1.47%) of 68 (imputed) surveyed radiotherapy department have answered to offer heart-sparing used in prone [13]. In Ghent University prone WBI and RNI have been adopted in routinary practice with DIBH technique in left sided BC [14]. In Italy prone positioning is still a process included in the ABPI trials using GammaPod® [15,16]. In Ontario, among 3894 patients receiving unilateral whole breast radiotherapy in 2014–2018 at the Sunnybrook Health Sciences Centre, 80 (2.1%) were treated prone [17]. From the Michigan Radiation Oncology Quality Consortium, only 200 (4.3%) of 4688 breast cancer patients were treated prone [18]. From a database review in Brisbane, Australia, only 13 (1.8%) patients actually have been reported to be treated with prone breast radiotherapy for 708 supine treatments [19].

2. Positioning Customised Immobilisation Systems

2.1. The Gravitational Dose Shift Effect in Prone Position

When comparing the dose distribution in supine vs prone WBI, the feature that immediately catches the eye is the role of gravitational forces within the anatomical down shift of the breast and the chest making a very important difference in toxicity. In supine WBI, the breast-capped lung and heart, the intramammary skin fold and the spread out breast are encompassed in prone WBI with uncapped lung and heart, outstretched skin folds and elongated breast leading to superior dose distribution, less skin reaction, cosmetic changes and much lower dose to the lung and probably to the heart. Since 1990s, a substantial number of trials were conducted (mostly in the USA) involving several BC patient series to assess the advantage of this gravitational dose shift in terms of dosimetry and toxicity when using prone position rather than supine WBI in the case of large and pendulous breasts and left sided breast cancer to resolve the inhomogeneity dose deposition effects causing hot spot deposition and breast fold inflammation. A first simulation of this effect was showed by Bieri et al on an anthropometric phantom treated in the supine and prone position reporting a significantly reduced integral lung, bone marrow, and cardiac doses with prone tangents [20]. Among pioneers study, Merchant et al. demonstrated a reduction in dose inhomogeneity by approximately 15% compared with supine position using tangents fields in women with pendulous breasts irradiated in the prone position [6]. For these large breasted women, the high dose region at the base of the breast ranged from 102%–103% in the prone position to 116%–118% in the supine position. Identical

dosimetric advantages were confirmed by a retrospective analysis of Mckinnon et al. The analysis revealed a homogeneous coverage of breast tissue by the prescribed dose. The high dose regions were displaced at the posterior medial and lateral borders and at a region close to the most anterior point of the breast. The dose at these points did not exceed 113%, and the average maximum dose was 107.6% [21]. In turn, a study of Grann et al reported a remarkable cosmetic score outcome and data on local control and survival similar to the expected outcomes with conventional supine tangents) [22]. Given this background, Stegman et al. conducted a retrospective study on 254 early BC women treated with prone WBI. Initially, the protocol included only patients with large, pendulous breasts; subsequently, patients with significant comorbid cardiopulmonary disease with left BC, extensive tobacco abuse, and patient or physician preference were enrolled [23]. Dosimetric analysis was not performed, however no exacerbations of the comorbid disease in these patients were observed neither radiation pneumonitis were reported. Moreover, studies conducted by Formenti et al. have contributed considerably to show the gravity advantages in dosimetry. Data on 91 treated patients were reported revealing the feasibility of achieving OAR's sparing according to the protocol prescription for the heart limiting 5% of volume to receive ≥ 18 Gy and $\leq 10\%$ of IL volume to receive ≥ 20 Gy [24,25]. All these studies have been performed using several different customized prone immobilization devices which have been evolved overtime to implement two different prone conditions: dive and crawl position. (Figure 1)

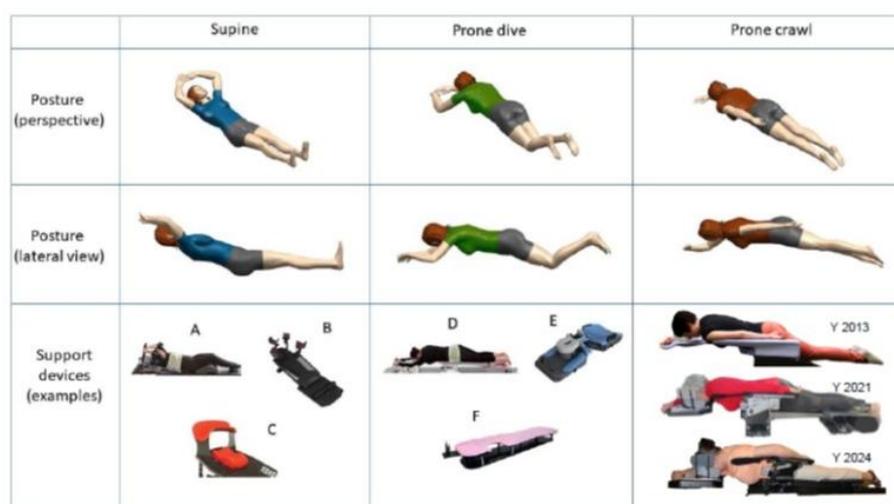


Figure 1. The figure presents the different positions : supine , prone dive and prone crawl with the treatment support . A-B-C for supine breast board ; D-E-F for prone dive (F is the first prototype) ; y 2013- y 2021- 2024 for prone crawl by the Ghent group. (Permission by W. De Neeve).

2.2. The Prototypes for Prone-Dive Position

Dive position is the most common modality to drive prone WBI on a customized device with arms blocked ahead, the legs on cushion wedges and the treated breast hanging down through an open window in the table. The first prone-breast board prototype was tested at the Memorial Sloan-Kettering Cancer Center (MSKCC) by Merchant et al. using a customised flat or curved table to be mounted on a simulator coach and linac table [6]. The device consisted of an opening in a wooden platform top through which the treated breast hanged along with a portion of the ipsilateral chest wall. The medial and lateral borders of the breast tissue as determined clinically, had to be included within the field of the tangential parallel-opposed photon beams. The ipsilateral arm was placed at the side or above the head. At University of Southern California (USC), Formenti et al. reported their first experience using a customised platform to adopt a radiosurgery-like technique for a partial breast irradiation in the prone position [24]. The board was a home-built solid wood platform containing a system of removable concentric inserts at the level of the breast. Each insert consisted of several concentric rings to accommodate breasts with different sizes. In the NY experience, this

device was fitted for whole breast prone irradiation to assure a precise, reproducible, and comfortable set up. The side bar of the USC prototype was removed. The arms were up sided. To improve patient comfort, a prone mattress comprising a thick memory foam layer placed on top of 12.5 cm Styrofoam was applied [25]. This complex ensured reproducibility through an equal degree of compression by the patient weight. This study also described solutions for a comfortable and better set up reproducibility, such as a cushion wedge to push away the contralateral breast. In the trial of Stegman, a prone board with adjustable aperture and handgrip with a Styrofoam wedge for the contralateral breast was provided. Mckinnon et al developed a set of equipment that enabled the treated breast to be suspended between two 20 cm Styrofoam blocks. There was a gap of approximately 15 cm between the two blocks. It was adjusted marginally depending on the size of the breast. A board to support and remove the contralateral breast from the treatment beam was placed across the two Styrofoam blocks. The arms were placed forward the head in prone dive and the head was turned to the most comfortable side while a kneefix cushion was placed under the ankles for comfort and stability [23]. Another solution for prone dive was proposed by Lakosi et al. This system satisfied patient comfort and reported data on residual-intrafractional errors in prone positioning with daily cone-beam computed tomography (CT). The novelty of this system consisted of three components: the cranial part immobilised the head and arms, with the head resting on a forehead–chin bracket, arms braced at the elbows, and hands gripping a pair of handlebars. In the middle part of the thoracic portion, the index breast was suspended freely through a cut-out while the contralateral thorax was supported by a horizontal board. The caudal portion was designed to support the pelvis and lower extremities with thermoplastic mask fixation. The mean overall patient comfort score was good. The lowest comfort score was achieved for the ribs, whereas the best score was reported for mask discomfort. Interestingly, the staff's scores were generally lower than the patient comfort scores [26].

2.3. The Prone-Crawl Coach

The prone crawl coach is a novelty because it yields an open access to the breast and II axillary levels with the breast pending in the vacuum space and no arm interposition. In comparison with prone dive, this position enhances patients comfort, permits access to respiratory orifices as demonstrated in patients cured in Intensive Care [27]. Further it delivers lesser scatter dose due the easy access to the treated breast using smaller beam apertures and more separation between breast and OAR's. As a result, it has been assessed that in patients requiring breast radiotherapy only, prone crawl position leads to a reduction of acute toxicity and cosmetic changes , 70%-80% reduction of lung dose > 2% reduction of long-term lung cancer risk.~15% reduction of heart dose in left-side RT. In patients requiring breast and lymph node radiotherapy the benefit consists of ~40% reduction of lung dose, ~20% reduction of heart dose in left-side RT, ~20% reduction of contralateral breast dose [28]. These data come from the experiences of Ghent University radiation oncologists who have investigated the comfort and effectiveness of this new prone position with the arm on the treated side alongside the body and the other arm on the contralateral side above the head. It is called crawl position because it resembles a phase of crawl swimming. A new comfortable Crawl coach (CrC) to support this new position has been made to irradiate the breast, chest wall, and regional lymph nodes. The contralateral breast is obstructed by a customised red bra with black strips on laterals to fix the green alignment laser [28].Compared with the commonly used prone position with bilateral arm elevation, the crawl position has been validated for better comfort, stability in positioning, and set up precision. Importantly it permits a wide range of beam directions in the coronal and near-sagittal planes that reach the breast and regional lymph nodes without passing through components of the crawl positioning device. To assess the precision of the setup, the consumed time, and patient comfort, the authors conducted a cross-over trial on 10 left BC patients using a standard prone breast board (BB) device and the customised prone device for crawl (CrC) [29]. The set up errors were evaluated by cone beam CT. The comfort, preference, and set up time (SUT) were also investigated through a customized questionnaire. Compared with a control group on a standard prone device, the

LL shift spread reduced significantly. The median SUT was similar at least 3 min for all the groups. The CrC improved the precision and comfort compared with BB. To test the comfort and patient preference, a questionnaire was administered at the time of simulation to each patient [30]. To evaluate the pressure/tension and pain on several anatomical points, a score on the continuous visual-analogue scale was provided. After treatment, none of the patients who answered the questions and returned the form experienced pain pressure, sliding sensation, or tension on the crawl couch. Meanwhile, this was the case for a few patients on the standard BB. When asked to indicate which support device they preferred, 9 out of 10 patients preferred the crawl couch. Compared with the standard prone positioning, the use of the novel crawl couch improved the positioning precision for prone WBI [29].

3. Advantages of Prone vs. Supine Position WBI

3.1. Breast Size and Acute Toxicity

The acute and late skin toxicity in women with large breast sizes irradiated in supine decubitus is a significant concern owing to the hot spot deposition in inframammary fold and irregular thickness of breast parenchyma. All studies conducted on prone position WBI have revealed an improvement in dose homogeneity resulting in a reduced rate of acute skin toxicity in large and pendulous breasts. In the study of Griems [31], comparing the two positions in 15 patients with varying breast sizes, the authors observed a significant decrease in the volume of the breast receiving more than 105% of the prescribed dose in prone set. Furthermore, the homogeneity dose distribution was similar regardless of the breast sizes (pendulous or otherwise). This effect resulted in a low skin toxicity while in the study of Mckinnon, desquamation developed in 50% of the patients.

In a study comparing supine and prone plans in five patients with moderate-to-large breasts, Kurtman et al. reported decreased hot-spots in four cases [32]. As a consequence of the achievement of a better dose homogeneity, limited G3–G4 acute and chronic toxicities were observed in this series. In the study of Stegman, the rate of acute G2–G3 dermatitis was 16% and 2%, respectively. Meanwhile, chronic G2–G3 dermatitis at two years follow up was 2.8% and 1.6%, respectively. Although the patients included in this series tended to have larger breasts, the observed rates of chronic toxicity were similar to those reported in the literature for standard fractionation and supine-WBI treatment of women with an equal average breast size. The data provided by Vesprini et al in a phase-3 multicentre single-blind randomised trial on 378 women with large breast sizes (bra band ≥ 40 in, and/or $\geq D$ cup) in the prone vs. supine positions yielded similar conclusions. The desquamation rate, as the most monitored observation, was statistically significantly higher in patients treated in the supine position compared with the prone position ($P = .002$). This result was verified by multivariable analysis (OR, 1.99; 95% CI, 1.48–2.66; $P < .001$), in conjunction with other independent factors: use of boost (OR, 2.71; 95% CI, 1.95–3.77; $P < .001$), extended fractionation (OR, 2.85; 95% CI, 1.41–5.79; $P = .004$), and bra size (OR, 2.56; 95% CI, 1.50–4.37; $P < .001$) [32]. By the experiences on crawl prone positioning, authors found a low toxicity score. The toxicity was scored before WBI, every six months in the first two years after WBI, and annually thereafter according to the Late Effects of Normal Tissue-Subjective, Objective, Medical Management, and Analytical Evaluation (LENT-SOMA) scale. Initially, no significant differences in physician-assessed toxicity were observed except for pigmentation variations ($P = .005$), in favour of prone positioning. In the longitudinal analysis of grade 2 toxicity, prone positioning resulted in a lower overall toxicity than that for supine positioning ($P = .005$) [29]. In the overview of the five-year photographic assessment, no significant difference in deterioration of breast cosmesis was observed between the groups at five years after radiation therapy [30].

3.2. Left-Sided Breast Prone Positioning Irradiation

Owing to concerns that radiation in the supine position is ‘more damaging to the heart’ in left-sided BC as shown by Darby et al. [6], several attempts on prone versus supine decubitus have been

conducted as in dive as in crawl positions to demonstrate its usefulness in sparing heart in left-sided WBI [34]. However, not all of them reached a strong agreement. Griem et al. performed a dosimetric analysis comparing dose-volume histograms (DVHs) for target homogeneity coverage, ipsilateral breast and contralateral breast volumes, ipsilateral and contralateral lung volumes, and heart volumes in 15 patients studied with plans with supine and prone positioning (seven right and eight left) and different breast sizes. Conformal 3D RT with tangential wedged photons beams was delivered only to the breast. As a result, the volume of breast receiving $> 5\%$ of the prescribed dose was significantly less in the prone position ($p = 0.0074$). The average volume of ipsilateral lung receiving > 10 Gy and > 20 Gy was significantly less in the prone position. In particular, the percentage volumes of lung receiving ≥ 10 Gy and ≥ 20 Gy were significantly higher in the supine position for all the patients with left-sided lesions ($p = 0.0001$). But the integral dose delivered to the contralateral breast was not significantly different ($p = 0.6072$), as well as the V30 Gy and V20 Gy of heart ($p = 1.000$) [31]. Of course, the explanation for these unforeseen values is related to the anterior displacement of heart in the chest with the prone position, thus the distance between the heart and the chest wall comes short. The measurements of this displacement has been quantified by Chino et al. [35]. They compared the intrathoracic location of the heart in the prone and supine positions in 16 patients treated for left BC in free breathing. For each case, the distance between the heart and chest wall at nine points in three axial levels of the sternum in both supine CT and prone MRI were calculated. At each axial level, measurements were captured at the left sternal border, lateral extent of the heart, and midpoint. By this analysis, a systematic displacement of the lateral and superior border of the heart closer to the chest wall in the prone vs. supine position (mean displacement 19 mm (95% confidence interval 13.7–25.1 mm, $p < 0.001$) was observed. Meanwhile, no difference was observed in the medial and inferior locations, which remained fixed. It is noteworthy that a reduction in volume of the lung interposed between the heart and chest wall in prone evaluation was demonstrated. A mean decrease of 22 mL ($p < 0.001$ for difference) was observed. This indicated how these observations could have an adverse impact in situations in which the high-risk target containing tissues are included on the chest wall or deeply in the breast. Positive observations have been provided recently by a retrospective analysis conducted on 524 left-sided BC patients treated with hypofractionated radiotherapy in the prone position. The results of this study were compared with literature data from supine treatments using the same hypofractionated schedule. This study verified the advantage of prone positioning in reducing the dose to the heart and LADCA. It identified the dosimetric parameters differences converted in EQD2 in terms of mean values (\pm SD) for MHD = 0.69 Gy (± 0.19), LAD Dmean = 2.20 Gy (± 0.68), and LAD Dmax = 4.44 Gy 41 (± 1.82) [36].

Going to the crawl prone positioning studies, comparison revealed that the while the target volume coverage was not different between the prone and supine positions, the dose to organ at risks were reduced significantly ($P < 0.05$) in the prone position for the ipsilateral lung (Dmean, D2, V5, V10, V20, V30), contralateral lung (Dmean, D2), contralateral breast (Dmean, D2, and for total axillary WB + LNI also V5), thyroid (Dmean, D2, V5, V10, V20, V30), oesophagus (Dmean, and for partial axillary WB + LNI also D2 and V5), skin (D2, and for partial axillary WB + LNI V105 and V107). There were no significant differences in the heart and humeral head doses. [28–30].

3.3. *Supine-Free Breathing (S-FB) Versus Prone-Free Breathing (P-FB)*

As reported above, in prone positioning, the heart displacement down to the chest yields an uncertain advantage for heart dosimetry in left-sided breast radiotherapy within the tangential fields. The difference between S-FB and P-FB breathing has been questioned by a meta-analysis including 751 patients from 19 observational studies. By a comparison between S-FB and P-FB, a significant advantage in OAR's sparing was observed in P-FB concerning the heart dose in terms of Dmean ($p < .00009$), Dmax ($p < .00001$), V5 and V20 ($P = .001$), LADCA Dmean ($P = .005$), and Dmax ($P = .03$), V40 ($P = .01$). For the lung, similar outcomes were recorded ($p < .00001$) for ILL Dmean, Dmax, V5, and V20 in favour of P-FB. However, no significant difference in target coverage between the S-FB and P-FB groups ($P = .66$) was observed [37].

3.4. Supine Breath Hold Versus Prone-Free Breathing

A randomised study -UK HeartSpare Study -comparing voluntary deep inspiration breath hold (VBH) versus free breathing prone technique was conducted by Bartlett et al to assess cardiac dosimetry differences on 34 enrolled patients who had an estimated breast volume > 750 cm³ requiring only WBI. Tangential fields were applied and moderate hypofractionation 40 Gy in 15 frs. was delivered. Patients were simulated in prone position on an Orfit AIO Solution[®] prone breast board. Patients were randomised to receive this technique or the Voluntary Breath hold technique (VBH) for the first seven fractions before switching techniques in the last part of the treatment. As a result, all cardiac dose parameters were statistically lower in the VBH than in prone treatment. Heart NTD_{mean} was 0.44 [0.38-0.51] vs [0.66 0.61-0.71] (p <0.001) ; LAD NTD_{mean} was 2.9 [1.8-3.9] and 7.8 [6.4-9.2] (p <0.001) respectively.; LAD_{max} was 21.0 [15.8-26.2] vs 36.8 [35.2-38.4] respectively. Ipsilateral and whole lung NTD_{mean} were significant lower in prone position than VBH :3.73[3.42 -4.04] vs 0.34 [0.27-0.42] (p <0.001) respectively. Mean contralateral breast dose was lower in VBH than Prone : 0.10 [0.08-0.11] vs 0.33 [0.23-0.43] (p <0.001). Given this result, the study was stopped early., concluding that supine VBH is advantageous and time sparing [38].

4. RT Advanced Techniques with DIBH in Prone Positioning

4.1. Prone DIBH Experiences

Given the well acknowledged role of DIBH in reducing the dose to the heart, LADCA, and ILL in left-side BC in supine treatments regardless of the fractionation [39], it is reasonable to provide this modality in prone positioning. Thus prone DIBH combining the gravitational effect on anatomy with the increased distance between heart and breast may address the problem to reduce heart dose in prone position. In the previous meta-analysis, the comparison between P-FB and S-DIBH was reported only within the two studies [37]. In the study of Mulliez et al., S-DIBH reduced the dose of heart (P < .001), and P-FB reduced that of LADCA and ILL (P < .001) [40]. In the study of Saini et al., there was no significant difference in heart and LADCA dose effect between the two groups. while for P-FB, the ILL dose reduction was significant (P < .001). Finally, comparing P-DIBH with S-DIBH, P-DIBH showed a dosimetric advantage in heart, LADCA, and ILL; (p < .001) in both the studies. Although the LADCA dose had no significant statistical difference in Saini's study, its value in P-DIBH was less than that in S-DIBH [41].

In regard to studies of Mulliez, in a first dosimetric report on DIBH in prone position for left-sided WBI, they demonstrated the ability of this technique to optimize heart dose. They conducted a first explorative study showing a clear advantage in heart dose sparing using DIBH in prone positioning on left-sided whole breast irradiation. Twelve patients underwent CT-simulation in supine shallow breathing (SB), supine DIBH, prone SB, and prone DIBH. A validation cohort of 38 patients received prone SB and prone DIBH CT-scans. The final 30 patients were approved for prone DIBH treatment. WBI was planned with a prescription dose of 40.05 Gy. As a result, the dose coverage index was 91.1 ± 3.3% for supine SB (explorative group), 91.2 ± 3.7% for supine DIBH (explorative group), 93.3 ± 3.7% for prone SB (all patients), and 93.0 ± 3.9% for prone DIBH (all patients). It did not differ significantly. In the explorative study, the authors observed that prone DIBH was at least as favourable as supine DIBH for heart and LAD sparing. Then, heart dose/volume results of the explorative study were reproduced within a validation trial. The planning goal of D_{max} < 5 Gy and D_{mean} < 1 Gy to the contralateral breast was obtained for all the position. The reductions in heart D_{mean} with prone DIBH compared with prone SB for breast volume less than 750 cc (18 patients), between 750 and 1500 cc (22 patients), and larger than 1500 cc (10 patients) were 1.3 (±0.9 Gy), 0.7 (±0.7 Gy), and 0.4 (±0.4 Gy), respectively. Moreover, the LADCA D_{mean} and D_{max} and the lung doses also reduced. A following trial was conducted on 51 early-stage left-sided BC patients treated by WBI after breast conserving surgery [41]. All the patients consecutively underwent CT-simulation in prone SB and DIBH. The volumes of the breast, heart, internal mammary lymph nodes (IMLNs), and both the lungs were calculated and compared between prone SB and DIBH. The distances of the

heart to the irradiated breast were analysed using breast–heart distance–volume histograms (DiVHs) for each patient. By the rigid co-registration of a prone positioned patient in SB and DIBH, the matching showed quantitative volume variations, centroid shifts, elongations, and overlap indices for the ipsilateral breast, clips, IMLN, heart, and lungs in favour of prone DIBH vs. SB. Prone DIBH decreased the heart volume by 4.3%, thus achieving a medial, posterior, and caudal centroid heart shift. According to the breast–heart dDiVH, DIBH and SB decrease the volume of the heart within smaller distances to the breast and becomes statistically significant ($p < 0.05$) between 0.7 and 10.3 cm for the breast [42].

4.2. Deep Inspiration BH in Crawl Prone Position

The group in Ghent validated the dosimetric advantages of DIBH in the crawl (CrC) position RT with photons and protons vs Shallow Breathing(SB). Thirty one patients with invasive carcinoma of the left breast and pathologically verified positive lymph node status were included in this study [42]. The patients were positioned on the prone crawl breast couch; DIBH was monitored using respiresens magnetic sensors placed on the surface of the breast couch and lateral thoracic wall. The patients underwent two CT scans for radiotherapy planning: first in a short DIBH of approximately 15 s and subsequently in SB. PTV also included axillary level II–IV lymph nodes and the ipsilateral mammary internal (MI) lymph nodes. For photon plan optimisation, a non-coplanar multiple overlying short arc VMAT technique was used in order to achieve optimal beam directions and a lower-dose spread to the OARs. The dose per fraction to the breast, level II–IV axillary, and ipsilateral MI lymph node regions was 2.67 Gy for photons and 2.67 Gy RBE/fraction for protons. As a result, the dose HI was 13.1% for photon DIBH, 12.8% for photon SB, 8.80% for proton DIBH, and 9.38% for proton SB. The differences in HI between photon and proton plans were significant for SB ($p = 0.002$) and DIBH ($p = 0.005$). The dose objectives were satisfied for all the targets in all the plans. Compared with SB, the DIBH-technique significantly decreased the mean dose to the heart in both photon and proton plans. The mean heart dose reduction in DIBH (compared with SB) for photon and proton was on average 2.0 Gy (range: -1.0–3.5) and 0.56 Gy RBE (range: 0.1–1.1), respectively. DIBH also resulted in a significantly lower mean dose for the oesophagus for photons. However, this was not so for protons. On average, in the photon plans, the left lung mean dose decreased by approximately 13% with the use of DIBH. Meanwhile, in proton DIBH plans, the average mean left lung dose increased by approximately 21%. No significant difference was observed for proton or photon in the mean dose to the contralateral breast [43].

5. Reproducibility in DIBH Prone Positioning

Reproducibility in repeated DIBH is a challenging issue as in supine as in prone positioning. In the study of Muellez, 21 over-30 consecutive female left-sided BC patients were irradiated only on the breast with prone positioning on a modified prone BB in SB and DIBH. The patient's breathing motion was registered as described before. During simulation, one prone SB and two prone DIBH CT-scans were acquired. The first DIBH scan (DIBH1) was used for treatment purposes. The second scan (DIBH2), with adapted CT-scan parameters to minimise the radiation exposure to the patient, was used to verify the anatomical reproducibility of DIBH in the prone position. Delineation of the heart, both breasts, and lungs was performed on SB, DIBH1, and DIBH2. A rigid registration of the DIBH1 and DIBH2 CT-scans was performed to evaluate the anatomical reproducibility of the DIBH phase. DIBH1 and DIBH2 CT scans were combined based on the DICOM coordinates. The overlap index was calculated for the ipsilateral breast, heart, and both the lungs. The overlap index was defined as the intersection of the volumes on DIBH1 (VDIBH1) and DIBH2 (VDIBH2) divided by the volume on DIBH1 (VDIBH1): the higher the anatomical reproducibility, the higher was the overlap index. The average and standard deviation of the DIBH amplitudes and intra-breath hold instability were calculated for each treatment session to evaluate the intra-fraction DIBH reproducibility and instability. As a result, the population amplitude of the DIBH was four times larger than that of the SB. This effect revealed the capability of patients to perform a deep breath in the prone position. The

intra-fraction standard deviation of the DIBH amplitude was 1.0 ± 0.4 mm (range 0.5–1.9 mm). This experience illustrated the high reproducibility of breath hold amplitudes during one treatment fraction. The number of breath holds required to deliver the treatment ranged from four to seven, each lasting on average 16 ± 1 s. This resulted in a treatment time of 300 ± 69 s (range 231–445 s) [44]. Deseyne et al. simulated the feasibility and intra-fraction reproducibility of the repeated breath hold technique (RBH) in the prone position for cases requiring WB + RNI after breast conserving surgery. The patients were positioned in the prone position on the crawl couch. Each patient underwent a free breathing CT scan and a breath hold scan, as well as an additional low dose RBH scan to evaluate the positional and dosimetrical impact of RBH and failure to breath hold (FTBH). The RBH manoeuvre was monitored using two respiration magnetic sensors as described earlier. Whole breast, axillary levels II–IV (LNN II–IV), and mammary internal nodes (LNN MI) were the targets (TVs). The treatment was designed using multiple short non-coplanar VMAT arcs. The spatial overlap between contoured volumes on different scans using the Dice similarity coefficient (DSC) and overlap index (OI) were adopted to assess the differences. As a result, a significant absolute volume difference between BH and FTBH scans was recorded for the contralateral breast, heart, lungs, and level II ($P < 0.05$). With regard to the OARs, the LAD, oesophagus, and thyroid showed more variability in OI and DSC than the others. Coverages of TVs resulted in no significant dosimetric differences for RBH. In FTBH, there were numerically significant but clinically less relevant dosimetric differences for CTV WBI, LNN III, and LNN IV. Larger differences were apparent in D95 and D98 of LNN II and LNN MI. These also reduced significantly in FTBH. With regard to OARs, there were no relevant dosimetrical differences for RBH, with the exception of V30 to the thyroid. In FTBH, there were significant dose differences for all the OARs except for the thyroid and right lung [45].

6. Nodal RT in Prone Position

6.1. The Ghent University Group Guidelines

The group from Ghent University started from the existing ESTRO14 and PROCAB13 for supine position guidelines to define new guidelines for prone radiotherapy considering the anatomical differences between the two positions. Practically, 18 MRI and 9 CT datasets were evaluated to include the interpatient anatomical variability. The MRI scans in the supine position (SP) and prone crawl position (PCP) were used to indicate reference structures and delineate nodal targets according to the ESTRO and PROCAB supine position guidelines. From this comparison between the two positions, the ESTRO and PROCAB clinical target volume (CTV) borders that need to be adapted for PCP owing to the position shift of the reference structures was recorded. During the process of selecting new reference structures, the resulting PCP CTVs were compared routinely with the SP CTVs to ensure that similar structures (mainly the veins) were contained within the CTVs (steps 2 and 3). The cranial and dorsal border of level IV; lateral border of level III; and cranial, lateral, ventral and dorsal borders of level I were adapted from the ESTRO and PROCAB guidelines to obtain PCP specific guidelines. These new PCP-specific guidelines incorporate the anatomical variability between patients and are applicable conveniently and consistently even for individuals having limited previous experience with delineations in PCP [46].

6.2. New York Langone University Guidelines

This group conducted an adaptation of the RTOG BC delineation guidelines from supine to prone position (performed by two radiation oncologists and a breast radiologist). It considered the anatomic variations from supine to prone position in 43 patient representative cases treated in the prone position on breast. Level I and II axillae were defined on simulation CT scan compared with preoperative diagnostic supine imaging. The revised nodal contours were reviewed by an expanded expert multidisciplinary panel to achieve a consensus to create an atlas specifically for CT scan nodal delineation in the prone position. For level II, the cranial, posterior, lateral, and medial borders remained unaltered. Meanwhile, the anterior and caudal borders were revised to better include the

intrapectoral and subpectoral nodes more caudal to where the axillary vessels cross the lateral edge of the pectoralis minor muscle. For level I, the cranio-caudal borders remained unaltered, whereas the other borders were revised due to difference in positions of landmarks between those of supine and prone [47].

6.3. Regional Lymph Node Irradiation

Coverage of axillary lymph nodes in prone position is another challenging issue as questioned by Haffty in a commentary review [48]. Several studies have verified if nodal irradiation in prone positioning is feasible and effective, but a preliminary experience conducted by Alonso-Basanta et al in a group of 20 breast cancer patients didn't show a dosimetric coverage of this volume. Patients underwent CT simulation in the supine and prone positions to assess whether a better coverage of target tissues or a better sparing of normal tissue was feasible using standard tangential technique. As a result, in both position, treatment of the nodal regions was inadequate. On average, the mean dose to the nodal regions for levels I-III was 50% less in the prone as compared with the supine position. The mean ipsilateral lung volume receiving 95% of the prescribed dose was 6.3% in the supine position compared to 0.43% in the prone position. When planned supine, the mean heart volume receiving 30 Gy was 0.56% compared with 0.30% in the prone position, suggesting that a supine setup should be chosen if the axillary nodes had to be irradiated [49].

Before the constitution of guidelines, a prospective trial of prone radiation therapy to the breast, postmastectomy chest wall, and supraclavicular and level III axillary lymph nodes was conducted on 69 patients with stage IB-IIIa BC. A dose of 40.5 Gy/15 fractions with a concomitant daily boost to the tumour bed of 0.5 Gy (total dose, 48 Gy) was prescribed using 3-IMRT fields. A dosimetric comparison between prone protocol and non-protocol conventional three-field/four-field supine plans was performed to evaluate the dose to the heart and lungs. As a result, the coverage of the breast/tumour bed and chest wall satisfied the established dosimetric constraints in all the cases. This revealed a significantly decreased lung V10 Gy and heart V5 Gy doses in prone plans. PTV nodes V38.5 Gy \geq 95% was achieved in all except 10% of case, The main acute toxicity was G1 radiation dermatitis occurring in almost all the patients. Meanwhile, none experienced grade 2 acute skin toxicity. Grade 1 lymphedema was the most common side effect, and an excellent/good score for cosmesis was obtained [50].

A phase 1/2 trial for stage IB-IIa BC was conducted by Purwuani et al. on 97 patients using a hybrid 3D-IMRT technique and moderate hypofractionated radiotherapy after lumpectomy or mastectomy with and without nodal areas. The target volume coverage and normal tissue goals with the rate of prone plans were achieved with V48 Gy \geq 98% in 92% of the patients, breast V40.5 Gy \geq 95% was permitted for 98% of the patients, and nodal V38.5 Gy \geq 95 in 89% of the cases. The constraints to the OARs were also satisfied. No acute toxicity over G2 was recorded. After a median follow-up of eight years, grade 2-3 late toxicity was recorded in 23% of the treated patients. No chest wall or nodal recurrence was observed in the subsequent follow up. At a median follow-up of eight years, grade 2-3 late toxicity was 23% for prone patients [51].

A first retrospective study was conducted by Speleers on 10 left-sided BC patients with invasive carcinoma of the breast and pathologically verified positive lymph node status treated on nodal areas. Six patients were scanned in the supine and prone crawl positions and four patients only in the prone crawl position on the prone crawl breast couch. The target consisted of the breast (WBI), level II-III axillary (AxII-III), inter-pectoral, peri-clavicular (PC), and internal mammary (IM) lymph node regions. The delineation for prone nodal area was performed according to the guidelines as before. Plans were formulated using a supine coplanar or prone non-coplanar multiple overlying partial arc VMAT technique. IMPT was used, with simultaneous optimisation of all the spots for all the fields. A median dose of 40.05 Gy (GyRBE) in 15 fractions was prescribed to the optimisation structures related to PTV-WBI, PTV-PC, and PTV-IM. The objective was to have 95% of the volumes covered with at least 95% of the prescribed dose (i.e. 38 Gy) and at most 5% receiving 105% of the prescribed dose (i.e. 42 Gy). The dose objectives were achieved for PTV-WBI, PTV-PC, and PTV-MI in all the

plans. The comparison study between protons and photons did not reveal significant differences between the photon and proton plans with regard to the maximum PTV-WBI and PTV-PC doses. The minimum dose to the target volumes was higher in the proton plans than in the photon plans. Comparable maximum and higher minimum target doses resulted in a better dose-homogeneity for the proton plans than for the photon plans in the supine and prone crawl positions. The mean doses to the OARs were lower for prone crawl than for the supine positions and for proton than for the photon plans. The lowest average mean thyroid dose was obtained in the prone crawl photon plans (statistically significant versus all the other plans). The lowest average mean and D02 oesophageal dose was obtained in the supine proton and supine photon plans, respectively. The coverage of the breast and nodal targets was achieved equally in the supine and prone crawl positions. However, the minimum dose in the proton plans was higher for all the targets. This resulted in a better dose homogeneity than in photon plans in the supine and prone crawl positions [52].

7. Heavy Particle RT Supine vs. Prone Positioning

More recently, treatments with heavy particles such as intensity-modulated proton therapy (IMPT), proton arc therapy (PAT), intensity-modulated carbon-ion therapy (IMCT), and carbon arc therapy (CAT) have expanded the treatment scenario over the conventional rays (XRT). Heavy particles such as proton (PBT) and carbon-ion radiation (CIR) treatments have been implemented to minimise the dose deposition outside the target and an enhanced dosimetry with IMRT techniques. Kim et al. evaluated how these different modalities could influence the dosimetry in terms of the target and OAR's outcomes in supine versus prone positioning WBI and mitigate the long-term radiation side effects. They attempted to identify the dosimetrical differences by comparing the dose distribution in plans of six external beam WBI techniques (3D-CRT, VMAT, IMPT, PAT, IMCT, and CAT) in terms of the treatment position, breast size, heart's proximity to the breast, and risks associated with secondary cancer. Fourteen patients were enrolled and simulated with supine and prone positioning free breathing. The radiotherapy plans were evaluated with respect to the homogeneity index (HI) and Paddick conformity index (PCI) of the PTV. With regard to the prone position evaluations, the PTV's PCI was superior to that in the supine position for all the studied techniques. However, the supine position resulted in a statistically significant reduction in the mean heart dose for most treatment techniques. Furthermore, in the context of XRT, the prone position resulted in decreased mean lung dose and V20 values for the ipsilateral lung. In contrast, for PBT, these values remained minimal regardless of the patient's position. In terms of the separation between the PTV and OARs, the supine position resulted in a more substantial separation effect for the heart. Meanwhile, the prone position enabled the ipsilateral lung to separate more from the PTV compared with the supine position ($p < 0.05$). Secondary cancer risk estimation was quantified by a parameter defined EAR (excess absolute risk) for an individual exposed to radiation at a dose (D) at age (e) according to the Schneider's OED concept (organ equivalent dose for radiation induced cancer). As a result, PBT in supine not in prone position showed a reduced EAR than CIR for lungs and contralateral breast [53].

8. Prone Positioning in Right-Sided Breast Irradiation

It is reasonable to apply the same advantages of left prone WBI for right-sided breast RT in terms of the lowest radiation dose to non-target organs, regardless of the breast size. Prone positioning radiotherapy in right-sided BC should be less difficult because the distance between the tangential field's edge and the heart is less affected by how the gantry is adapted to the breast. Hence, its dosimetrical advantage is verified regardless of the pendulousness. A research by Fargier-Bochaton et al. assessed this issue by a retrospective study conducted in 2010–2013 on 146 patients with right BC treated in the prone position after a simulation with supine positioning. A penalty score was computed from the mean absolute dose deviation to the heart, lungs, breasts, and tumour bed for each patient's supine and prone plans. The dosimetric advantage of prone positioning was assessed

by the reduction in penalty score from supine to prone. Compared with supine, prone reduced the penalty score in 119 patients (81.5%). The lung doses reduced by 70.8%: from 4.8 Gy supine to 1.4 Gy prone. Among the patient's characteristics, the only significant predictors were the breast volumes. However, no cut off could have been identified if prone had been less advantageous than supine. Prone was associated with a dosimetric advantage in most patients. Thus, the option to be treated in the prone position should be offered to right-sided BC patients [54].

9. Prone APBI

A high evidence level trials have shown the safety and effectiveness of APBI and not inferiority to WBI like the Florence trial [55] and the IMPORT LOW [56]. Thus prone APBI seem a promising modality to improve in this set but CTV delineation is a challenging issue and the use of MRI breast images could be helpful [57]. There are still uncertainties like tumor bed delineation despite the clips locations and safe margins to add. As suggested by Monten et al, the comparison with preoperative CT may be considered a marginal expenditure for improving accuracy and achieve a good balance between reduced dose and volume to comply with the APBI rationale [8]. The discussion of this topic is a future object of research.

10. Discussion

Given the assumption that there is no evidence that one positioning technique is superior to another, supine treatment remains the standard positioning in WBI, and DIBH is the best system to reduce the dose to the heart [39]. However, a valid alternative treatment positioning has been tested to address dose homogeneity, cosmesis, and skin toxicity in patients with large pendulous breasts other than to reduce the dose to the heart in left-sided breast irradiation. Prone decubitus has attracted a growing interest in these past 20 years. As reported by Haffty, when conducting a search on Pub Med 10 years before 2008, only approximately 20 reports relating to prone breast irradiation could be identified. Meanwhile, from 2008 to 2018, over 100 reports have been published [48]. This implies that prone positioning continues to be a highly noteworthy topic for investigation [57] like its adoption in APBI recently. The advantage of prone radiotherapy is due to the gravitational dose shift effect as a consequence of the anatomical shift of the treated breast hanging down far from lung and heart, leading to a better dose homogeneity mainly in pendulous large breasts. By reading the commentary by Haffty, reasonable criticisms have been made in terms of the uncertainties in set up reproducibility, true advantages of OAR sparing, and coverage of targets including nodal irradiation; however novel literature data show the solution of these criticisms and support the advantages of this positioning with advanced techniques. Prone positioning has been demonstrated to achieve better dosimetry in large and pendulous breasts mainly in obese women, wherein supine treatment could be challenging. Acute and chronic toxicity has been shown to be similar to or better than that for the supine position regardless of the breast size and fractionation. Customised immobilisation coaches have evolved to improve patients' treatment comfort and set up reproducibility. The position of the arms and head have been shifted from a dive position to a novel comfortable one similar to the swimming crawl position, which has been shown to permit IMRT with a wide range of beam directions in the coronal and near-sagittal planes that reach the breast and regional lymph nodes without passage through components of the crawl positioning device, regardless of photons or protons [6–10]. In regard to nodal irradiation, several attempts have been tried as in dive as in crawl position [14,29,30]. The axillary levels and chest wall are now well targeted in prone decubitus with a good dosimetric coverage and defined by a customised atlas with validated contouring guidelines [46,47]. However, the best achievement has been shown in the dosimetry for the heart and LADCA, owing to the experiences with prone DIBH, which have defied the odds [42–45]. A summary is shown in Table 1.

Table 1. In the table are summarised the most important topic and literature data supporting the prone position.

<i>Topic</i>	<i>Author/year</i>	<i>Technique/fractionation</i>	<i>Main outcomes</i>
Large and pendulous Breast	Merchant , IJROBP, 1994 [6]	Conventional fractionation, 2D	The high dose regions at the base of the breast, were reduced to 102–103% for the same women treated in the prone position
	Grann, IJROBP, 2000 [22]	Conventional fractionation, 3D	Skin erythema in 80% with Grade I or Grade II, breast edema in 72%. The mean overall cosmesis score was 9.37 (range, 8-10).
	Kurtman, Braz J Med Biol Res, 2003 [32]	Conventional fractionation, 3D	Mean irradiation doses reaching the ipsilateral lung were 8.3 ± 3.6 Gy in the supine position and 1.4 ± 1.0 Gy in the prone position ($p = 0.043$). The values for cardiac tissue were 4.6 ± 1.6 and 3.0 ± 1.7 Gy ($P = 0.079$), respectively.
	Formenti, JCO, 2007 [25]	Hypofractionation, IMRT	Prescription for heart limiting the 5% of volume to receive ≥ 18 Gy and $\leq 10\%$ of IL volume to receive ≥ 20 Gy were met in all patients
	Mckinnon, Breast, 2009 [21]	Conventional 3D fractionation	Grade 3 acute dermatitis and edema were each limited to 2% of patients. Chronic Grade 2 to 3 skin and subcutaneous tissue toxicities were reported in 4.4% and 13.7% of patients, respectively.
	Vesprini, JAMA, 2022 [33]	Conventional 3D fractionation Hypofractionation	Desquamation in the supine position compared with prone 39.6% vs [26.9%] $P = .002$).
<i>Topic</i>	<i>Author/year</i>	<i>Technique/fractionation</i>	<i>Main outcomes</i>
Advantages in Left side BC	Griem, IJROBP, 2003 [31]	Conventional fractionation, 2D	The average volume of lung receiving >10 Gy and >20 Gy was significantly less in the prone positions. ($p= 0.0001$). The integral dose delivered to the contralateral breast was not significantly different ($p = 0.6072$) as well as the V30 Gy and V20 Gy of heart ($p= 1.000$). No advantage in heart sparing.
	Deseyne, Sci Rep , 2017 [14]	Hypofractionation, IMRT, Crawl position	Reduction doses ($P < 0.05$) for ipsilateral lung , contralateral breast , thyroid , oesophagus skin No significant differences for heart and humeral head doses

Lai, 2021 Medicine [37]	Meta-analysis	Advantage in P-FB for heart : D _{mean} (p <.00009), D _{max} (p <.00001), V5 and V20 (P = .001), LADCA D _{mean} (P=.005), D _{max} (P=.03), V40 (P=.01). For lung : ILL D _{mean} , D _{max} , V5 and V20 (p <.00001)
Gregucci, Cancers, 2025 [36]	Hypofractionation, IMRT	Reduced dose to heart and LADCA according dosimetric parametersdifferences converted in EQD2 in terms of mean values (±SD) for MHD = 0.69 Gy (±0.19); LAD Dmean = 2.20 Gy (±0.68); LAD Dmax = 4.44 Gy 41 (±1.82)

11. Conclusions

Convincing evidences of the advantage of this positioning in WBI have been provided to make prone crawl positioning more convenient than dive prone position and the misconceptions regarding prone positioning as a time spending modality has also been dispelled. Undoubtedly it requires a complete agreement by the radiation team for collaboration at many levels to address the challenges of implementing prone set up, which include the patient comfort and precision in set ups with customised immobilisation devices. Prone APBI is another issue under investigation with promising results [57]. Although these advances, there is a paradox between the growing evidence on benefit and weak clinical use of prone treatment because supine treatment still remains the gold standard position treatment.

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