

Review

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Review

Alternative Treatment Positions over Supine in Adjuvant Whole Breast RT: Prone, Lateral or What' Else? A Comprehensive Narrative Review

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Abstract

Whole breast radiotherapy in adjuvant breast cancer (BC) treatment is commonly delivered in supine positioning since more than 50 years ago. Its widespread use is related to the broad availability of simply and common breast board immobilization devices which exploit the natural recumbent position of the body with arms above the head, the good match with linac tables and well established set up procedures. However, several criticisms have been raised over time in case of scenarios like painful arm discomfort in patients with post-surgery arm or arthritic limitation, unfavorable chest geometry like pectus excavatum, large and pendulous breasts in obese women, cardiac morbidity in left sided BC. In these scenarios supine position seems very uncomfortable for patients and troublesome for radiation oncologists. Heart dosimetry in pectus excavatum (PE) and left sided breasts, breast size and shape matter when DIBH is not allowed. In fact, not all patients are suitable DIBH candidates because of the limiting factors like obesity or pulmonary morbidities. Thus, adjuvant whole breast radiotherapy in supine positioning could be very critical. Alternative positions have been analyzed in these last twenty years starting from a lot of trials testing prone positioning variants with and without DIBH, lateral decubitus or up-right standing radiotherapy. Customized immobilization devices have been developed to make these alternative positions more comfortable and consistent with beams angles arrangements and modern RT delivery avoiding collisions with the device or the Linac. To standardize the target delineation in these positions, customized guidelines have been also provided and recently several atlas-based segmentation processes have been provided to reduce bias by incorporating an interobserver quality analysis. Researches and a better recognition of new treatment position options in BC adjuvant therapy may provide more opportunities for a personalized radiotherapy mainly in that population not suitable for supine RT, to ensure them an appropriate, safe and comfortable treatment.

Keywords: breast cancer; radiotherapy; cardiac toxicity; obesity

1. Introduction

The absolute locoregional control and survival benefit of adjuvant radiotherapy in breast cancer has been well established through multiple randomized trials which have been conducted in supine position largely [1,2]. Technological advances have improved its therapeutic ratio and the quality of treatments providing more effective and safe RT delivery with breathing adaptation to reduce cardiac and lung doses as low as possible according to the ALARA principle [3].

Breast radiotherapy in terms of whole breast or partial breast are commonly delivered in supine decubitus. In this position the patient is immobilized recumbent on a treatment table with arms above the head while the beams are steered around them to arrange different treatment angles. However not all patients are suitable for this positioning because of unfavorable situations like post-surgery arm pain or arthritic arm impairments, pectus excavatum, left sided breast cancer, large and pendulous breast. After surgery, nearly 60% of patients experience severe acute postoperative pain, with incidence rates increasing with surgical complexity [4]. Pectus excavatum and left sided BC impact on radiation induced cardiac morbidities. Breast shape and size are to be taken into account for acute and late toxicities and cosmetic outcomes. DIBH has shown to offer a better trade-off between target coverage and OAR's dose sparing regardless all breast sizes [5], but not all women are best candidates for DIBH because of obesity or cardiopulmonary comorbidities [6]. Other strategies include different partial breast techniques like Linac based APBI [7], brachytherapy [8] or IORT [9], where available. Large breasts with cup size C and cup size $\geq$ D could be easily treated by IMRT-APBI, which has been demonstrated to offer a good reproducibility with a low rate of acute toxicity and excellent-good cosmetic outcome after median follow up of 3.2 years [10]. But several criticisms have to be taken into account in regard with clips locations and adequate margins to create a good compromise with the irradiated volume and the breast size. Higher body mass index and breast size are considered critical factors in supine RT because the set up on the linac table in obese women could be troublesome and breast pendulousness is related to high rate of acute toxicity and worst cosmetic outcome [11]. Thus, to ensure the RT delivery in these scenarios, several alternative treatment positions over supine have been investigated in these last twenty years. Prone positioning is the most studied treatment as a valuable solution for pendulous breasts or for left sided BC in attempt to improve dose homogeneity in the breast or reduce the toxicity to the breast, heart, LADCA and lung and in turn the second cancer risk [12,13]. However other positions have been tested like the lateral or the up-right position. This review explores all these new modalities in RT delivery for BC patients, their clinical differences in toxicity and their implications for a personalized radiotherapy in the BC population which are otherwise not compliant with supine positioning.

2. Material and Methods

This narrative review was performed by a comprehensive literature search of electronic databases, including PubMed and Google Scholar. Due to the nature of the topic and the heterogeneity of the related literature, a narrative review rather than systematic was considered more appropriate for this topic. The aim was to focus the radiation oncology community's interest on the current knowledge and emerging modalities related to position treatments alternative over the supine in conjunction with modern technologies rather than to perform a quantitative analysis.

The search strategy was conducted using a combination of key words, including "decubitus position BC radiotherapy", "standing technique for breast radiation", "lateral isocentering position", "prone position versus supine position", "upright positioning", "large or pendulous breast radiotherapy" "pectus excavatum and radiotherapy", ensuring the comprehensive identification of relevant studies. Titles and abstracts were screened for relevance, followed by a full-text review of selected studies. Studies of interests were included if they met the following criteria: (1) published in peer-reviewed journals, (2) written in English, (3) focused on BC adjuvant radiotherapy positioning and (4) published the last 20 years. This review is based solely on previously conducted research and does not include any new experiments or studies conducted by the authors. The arguments have been scheduled according to these issues: which conditions enable the supine WB irradiation? Which is the impact of breast size in radiation induced side effects to personalize the RT positioning? which dosimetric and clinical advantages over supine by prone positions, LD or Up-right standing? In answer to these issues all clinical studies including retrospective, randomized or metaanalyses referring to dosimetric experiences, safety data, clinical advantages by alternative positioning over supine were collected and analyzed. No automation tool was used during the literature search.

3. Unfavorable Factors for Supine RT Positioning

Arm impairment, unfavorable chest geometry, left laterality, breast shape and size can make very difficult the RT delivery in supine position. Severe acute postoperative pain is problematic for more than half of all breast surgery patients. It has been estimated that severe postoperative pain is symptomatic for 1 month in nearly 5% of breast surgery patients and 6-12 months in almost 10% of breast surgery patients [4]. Further obesity and older age may enhance this effect leading to an uncomfortable tolerance to treatment position [14]. Pectus excavatum (PE) is the most common congenital chest wall deformity, with an incidence of 1 in 300–1000 births [15]. It requires caution when WB RT in left sided BC should be delivered. In fact, it is acknowledged that in PE, heart and lungs may receive a greater radiation dose because of the concavity of the chest wall, leading to a greater risk of heart or pulmonary complications also with 3D conformal RT when considering that a higher incidence of RILI has been related to the V30 Gy using 3D tangential fields [16].

Several studies have investigated the real benefit of modern RT techniques like VMAT, IMRT or Tomotherapy in this set over a 3D conformal RT in terms of lower MHD or dose to ipsilateral lung, but they have failed with an increased cost of dose to contralateral breast and lung and in turn an increased risk of second cancers [17,18,19]. To solve the cardiac issue, a good compromise between a Target Prioritized 3D-CRT plan (TPP) and a OARs prioritized plan (OARPP) have been found effective in obtaining a median 3 Gy MHD in these patients although in case of severe chest deformity this option seems not suitable [20]. The risk of cardiac events related to the MHD over 4 Gy in left sided breast cancer has been well established by Darby [21], leading to the adoption of DIBH strategy to spare the heart as much as possible. Breast size and shape like large and pendulous breast are a big concern in terms of all the RT related toxicities (heart, lung, skin).

Actually, there are no definitive parameters to define adequately “large” the size of a big breast. An empiric and practical evaluation of the USA bra size cup $\geq D$ for large breasts is usually the most conventional feature as adopted in the study of Pignol et al [22]. In the past, the definition of large breast was based on the distance between the edges of the lateral and medial fields for a 2D technique, assuming a 25 cm of breast separation for large breast [23]. With the development of modern 3D treatments, a breast clinical targets volume (CTV) of $\geq 1.600 \text{ cm}^3$ have been reallocated to the large breast size definition [24]. Further, an evaluable and reproducible method to measure the breast is based on anthropometric measurements which takes into account the thickness of left and right axillary fat and nipple-to-pectoral muscle distance. This method has been found to correlate with the risk of skin toxicity related to breast irradiation [25]. It is well acknowledged that the size of the breast affects the final cosmetic outcome of radiation therapy treatment and could be an important limitation in delivery adjuvant RT safely as recognized by several investigators in many series including series of large breasted women treated in different institutions from the 90's to date. Studies by Harris et al [26], Clarke et al [27], Ray et al [28], Gray et al [29], have reported that large-breasted women or patients with a D size cup or greater have suffered from increased breast fibrosis and retraction when treated with supine radiation, showing worst overall cosmetic outcomes. In other studies, features like oedema, hyperpigmentation, teleangectasia, desquamation have been the main recorded side effects for a poor radiation induced cosmesis outcome in patients with large breast size [30]. Thus whole breast irradiation in supine as standard position seems very challenging in these patients. Indeed, in supine position the large breast tends to fall laterally and or superiorly causing a bolus effect on the skin due to the hot spots deposition in the inframammary folds or deep axilla where is typical the skin-on-skin contact. Given the widespread adoption of modern hypofractionated regimes, the role of hot spots in increasing skin toxicity should be accounted because of the well known phenomenon of the double-trouble and triple -trouble effects which could amplify the delivered effective dose [31, 32]. Moreover to ensure an adequate coverage of the posterior part of the breast volume, the breast cupped lung and heart in supine position may receive increased RT doses leading to late toxicity in terms of heart cardiac events and secondary malignancy risk [33]. The DIBH modality is the most effective solution to improve the dosimetry to heart and lung in supine, but when patient is not a suitable candidate, the issue of RT in left sided BC and in large breasts sized

patients still remains unsolved. Alternative solutions could be found in the treatment positioning modifications. Over the supine decubitus, three alternative positioning could be proposed: prone, isocentring lateral decubitus (ILD) and up-right standing or seated position. In this review we provide readers with effective insights into these alternative treatment positionings over supine assessing their usefulness and convenience to offer a personalized whole breast irradiation.

4. Prone Positioning

Prone positioning is the most tested option and still yields a growing interest widespread. The first expectation by this position has been to improve dose inhomogeneity in pendulous and large breasts; in turn it has also been tested in left sided breast irradiation to spare the heart and LADCA. In this position the irradiated breast hangs down through an opening in the plate of a customized immobilization device to be included in the tangential RT beams. Initial experiences have been carried out in prone dive position [34,35,36]. Later a new prone position, the so called “ prone crawl ”, have been provided, resulting more comfortable and effective also to include the nodal areas in the radiation fields [37]. Although the purpose to improve the dose homogeneity distribution in the breast's body has been reached, conflicting results have been achieved in regard with the advantage to heart, LADCA, ipsilateral lung (ILL) as summarized in a meta-analysis [38]. Thus many trials have been conducted to improve heart dosimetry comparing the prone position in shallow-free breathing and DIBH RT assessing the set up reproducibility with repeated breath hold [39]. At the beginning, only the breast has been considered the target to irradiate in prone decubitus; however the inclusion of nodal areas has been also attempted in dive and crawl modalities yielding good dosimetric reports. In dive position the study of Pursuwani et al has shown the feasibility to irradiate the nodal areas in prone position after lumpectomy or mastectomy on a group of 97 patients using a hybrid 3D-IMRT technique and moderate hypofractionated radiotherapy. The target volume coverages and normal tissue goals were reached in almost of cases. In fact, the $V_{48\text{ Gy}} \geq 98\%$ was allowed to 92% of cases, the breast $V_{40.5\text{ Gy}} \geq 95\%$ was recorded in 98% of the patients, and in 89% of the cases the nodal $V_{38.5\text{ Gy}} \geq 95\%$ was obtained [40]. The constraints to the OARs were also respected and the nodal contouring delineation was guided by internal guidelines [41]. Concerning the crawl position, the studies of Speleers et al conducted on a series of left-sided BC patients with invasive carcinoma of the breast and positive lymph node requiring nodal RT, have confirmed the feasibility to include over the breast, also the II-III axillary levels, the inter-pectoral, peri-clavicular, and internal mammary lymph node areas. The aim was to obtain the 95% of the volumes covered with at least 95% of the prescribed dose (i.e. 38 Gy) and not over the 5% receiving 105% of the prescribed dose (i.e. 42 Gy). The mean doses to the OARs were lower for prone crawl than for the supine positions. The coverage of the breast and nodal targets were similar in the supine and prone crawl positions [42]. Thus in crawl prone positioning the nodal irradiation has been safely allowed and conducted according validated guidelines taking into account the different position of axillary nodal levels [43]. After an internal validation of these guidelines, an atlas based segmentation in prone breast cancer radiation therapy has been developed to make quick and homogenous the nodal target delineation [44].

5. Lateral Decubitus Positioning

The breast irradiation in the lateral decubitus (LD) is a technique which has been introduced at the Institut Curie more than 30 years ago with the primary end point to improve the dose homogeneity in large and pendulous sized breasts [45]. By then, this technique has been found advantageous also for pectus excavatum [46]. The first pivotal trial was carried out by Frangois Baclesse in 1950's [47], then this modality was adopted until 1980's on the first 644 patients treated with a 2D RT [48]. Thereafter this treatment position has been improved with a 3D isocentring technique so called isocentring lateral decubitus (ILD), consisting of a 3D planning and portal images to assure the correct set-up [49]. In this position the whole breast gland is the target to be irradiated, while the nodal areas are excluded. Usually, the patient lies with the trunk rotated from one side to

the other in order to allow a treatment with an isocentring technique using two opposed photon beams tangent to the ribs wall and vertical to the breast. Initially RT was delivered with Co 60 unit at SSD of 80 cm; later the low megavoltage energies were adopted. In the historical experiences, the lateral field was delivered to the patient lying on the contralateral side to the treated breast; the ipsilateral arm had to be extended upward above the head in order to expose to the beam the breast volume. The treated breast was stretched over a support made of 3 cm lead built to protect the contralateral breast. The medial field was delivered to the patient lying on the ipsilateral side, with the ipsilateral arm below the head and the contralateral hand reclining the contralateral breast outside the beam. The breast was stretched on the treatment couch to obtain a homogeneous reduction of breast thickness which permitted a better dose distribution in the breast parenchyma [47, 48]. Later this positioning has been optimized with a reproducible set up within a dedicate immobilization system. Customized guidelines have been developed to guide the target delineation in this position [50]. The following contouring details have been incorporated into a neural network-based autocontouring algorithm which offers a practical, time-saving solution for breast cancer radiotherapy planning in this decubitus [51].

6. The Upright Standing Positions

This technique has been tested in obese women with high body index exceeding the weight limitation of the equipment; recently a novel system with rotating robotic chair with fixed gantry has been implemented using specific radiotherapy bras to smooth the inframammary fold. The first experience of upright standing RT was reported in 2010 by a team of radiation oncologists in Baltimore on an obese big woman with right breast cancer treated with breast conserving surgery, unable to be treated under the linac in recumbent position for weight limitation of the equipment. [52]. The patient kept up-right beyond the couch consisting of a carbon fiber SBRT body frame with the breast up on it to the level of the inframammary fold while keeping the ipsilateral arm behind her back and out of the field. As a mold, an aquaplast pelvic body cast was cut and molded over the breast. CT scan on the empty breast mold was conducted and planning was calculated on a tissue equivalent density in the mold. Treatment consisted of 3D conformal RT with two opposed tangential fields and conventional fractionation. The patient was treated without disruptions with a conventional fractionated RT. This modality has a limitation consisting of the inability to add a matching supraclavicular or axillary field, thus the nodal areas are not included. Recently this position has evolved into an upright patient positioning on a rotating, robotic chair within a gantry-less linac system [53]. Because in the seated position the breast naturally falls vertically down, it has been hypothesized a possible anatomical advantages resulting from an upright body posture, such as an increased lung volume and reduced breathing motion to exclude the use of breathing holding techniques [54,55]. Moreover, due to natural anatomical breast position on the chest with the skin to skin contact, to smooth the inframammary breast fold, several radiotherapy specialized bras have been successfully adopted obtaining at least a median 3 cm reduction of the skinfold. Moreover, the arm -up or down on the flanks position have been investigated in order to improve the patient arm comfort. [53]. However this technique is still working in progress.

7. Immobilization Devices

Customized immobilization devices have been built to improve patient's comfort, set up reproducibility, matching with modern RT delivery techniques without collisions with the equipment and or part of the patient's body.

7.1. Prone Immobilization Devices

Prone dive position is the most investigated position. In this position the head usually is resting on a forehead–chin bracket, the arms are braced at the elbows with the hands gripping a pair of handlebars; the treated breast is hanging through an opening on the top table while the contralateral

breast is stretched on a wedged cushion and the lower extremities are supported by a mattress [56]. At the beginning, the first devices consisted of a home-built wooden platform top with a hole through the breast was hanging along the chest wall to be included within the RT field of the tangential parallel-opposed beams; by then several customized immobilization device have been developed and modified overtime to make this position more comfortable and ensure a precise set up of the chest [57,59]. Another option which has been recently developed is the crawl prone position, so called because it mimics the crawl swimming position. In this position patient lies prone with the arm at the treated side alongside the body and the arm at the contralateral side above the head. A customized and very comfortable couch has been assembled to permit the irradiation not only of the breast, but also of the chest wall and regional lymph nodes using a vast range of beam directions in the coronal and near-sagittal planes with IMRT or VMAT, avoiding any kind of collisions with the device. This couch position has been validated in several trials by patient and physicians and it has been defined very comfortable and no time spending. DIBH systems are allowed to both prone modalities [60,61].

7.2. Lateral Decubitus

As described before, in the lateral decubitus the patient lies with the trunk rotated from one side to the other on a dedicated patient board (Techset®) with a back rest. A large elastic fabric band attached to supports using Velcro serves to move the contralateral breast out of the radiation fields. The patient lies on the side of the treated breast. A thin carbon breast rest of 6 or 7 cm height with angled sides is placed under the breast with its long edge along the lateral border of the breast. The surface of this support consists of a flat part where the breast is placed and a curved part adapted to the convexity of the thorax. The thickness of horizontal part is only 0.3 mm, allowing a good preservation of the skin by limiting the bolus effect. On the dorsal support, a vertical pole shaft is mounted to be used by the patient where to place the contralateral arm. There is no need to add a DIBH system to spare the heart [62].

7.3. Up-Right Positioning and Rotating System

Upright body positioning for breast radiotherapy has not been studied extensively. The first experience has been reported many years ago by Mouhiddin et al as described before in an obese woman not suitable for recumbent position treatment [52]. Recently there have been conducted a novel study investigating a patient position seated on a robotic rotating chair to deliver a seated upright breast RT modality. In this position the breast falls vertically down to the chest creating the inframammary fold which needs to be smoothed out using a specific RT bra. The arm position could be positioned up over the head or down on flanks, depending by the patient's compliance. The first trial has been conducted on the 'Eve' linac upright patient positioner from Leo Cancer Care Ltd ® (Horley, UK). This system consists of a backrest, seat pan, shin rest and heel stop, which can all be adjusted independently. The backrest can be angled at 0° (vertical) or forward/backward by 5°, 10° or 15°. The seat pan angle can be varied between 0 °C (horizontal, for a sitting position) and 60° (tipped towards the floor, to support a body position that is close to standing). The initial seat pan height is set according to the patient's lower limb length. The position of the shin rest and the heel stop are also adjusted individually, so that each patient's lower limbs can be comfortably immobilized. This system has been tested with photons and protons and it is still under investigation to assess how reducing set-up errors, how stabilize a better position of the upper body through custom-designed arm supports or which photon beam access [63]. As reported by Yoganathan et al, in this natural position of the thorax, the organ motion for intra-thoracic organs is more pronounced in cranio-caudal than in antero-posterior and medial-lateral directions, thus there is no need of breath control to spare heart or lung. Uncertainties in antero-posterior and medial-lateral directions influenced by respiratory motion have been measured resulting within 3 mm in 81% and within 5 mm in 91% of the patients tested in the up-right trial patients. These values seem not impact on heart or lung dosimetry; trial is still working progress [64].

8. Which True Benefits in Changing the Treatment Position?

The primary end point of these alternative positions has been to reduce the dose inhomogeneity in the breast parenchyma to achieve a less acute skin toxicity in the inframammary fold or in the axilla, obtaining a better cosmesis and low dose bath to OAR's at risk mainly in large and pendulous breasts, in pectus excavatum, left sided breast cancer, regardless of the fractionation schedules without compromising the target coverage and the disease control.

8.1. Dose Inhomogeneity and Toxicity

Prone Positions

A first experimental simulation on an anthropometric phantom performed by Bieri et al showed the effect of prone position over supine in reduction of the integral dose on OAR's to confirm a reduction its effect on low toxicity [65]. Merchant et al treating a group of BC patients with pendulous breasts in prone, compared with supine, recorded a substantial reduction of hot spots in prone accounting for 102%-103% in the prone position versus 116%-118% in the supine with a reduction in dose inhomogeneity in the target by approximately 15% compared with supine tangents [56]. In a retrospective analysis of Mckinnon et al, prone positioning yielded a reduction of hot spots within the 113% of the prescribed dose and the maximum average of 107.6%, recording no severe acute toxicity in the high dose regions displacing hot spots [66]. In the study of Grann et al a remarkable cosmetic score outcome with prone position was recorded due to an improved homogeneity in the prone treated large breasts whereas in supine the isodose distribution had shown the location of hot spots at the apex of the breast, and at the periphery of the breast over 20% in very large breast [67]. Kurtman et al when comparing the supine and prone plans in patients with large breasts, confirmed the reduction of hot-spots obtaining an improved dose homogeneity and few cases of Grade 3-4 acute and chronic toxicities [68]. In the retrospective study of Stegman et al conducted on 254 early BC women treated with prone WBI, Grade 3 acute dermatitis and edema occurred in the 2% of patients while chronic Grade 2 to 3 skin and subcutaneous tissue toxicities were reported in 4.4% and 13.7% of patients, respectively as a result a median hot-spots nearly 106% [69]. Further, in a phase-3 multicenter single-blind randomized trial on prone vs. supine position on 378 women with large breast sizes with a bra band ≥ 40 in, and/or $\geq D$ cup, Vesprini et al, showed that the desquamation rate was higher in the group of patients treated in the supine position ($p = .002$) regardless the fractionation schedules arm groups [70]. In addition, all the studies conducted by Formenti et al on prone hypofractionated radiotherapy in APBI or WBI, have provided robust data of good-excellent cosmesis using this position [71,72]. In the experiences conducted in crawl prone on breast or chest wall and nodal areas, as a result of improved homogeneity dose distribution, a low toxicity score on the LENT-SOMA scale has been recorded and then confirmed by a longitudinal analysis. As a result, for grade 2 toxicity, in prone positioning a lower overall toxicity than that for supine positioning ($p = 0.005$) has been shown [73]. Hypofractionation in 5 fractions over 10-12 days leads to significantly less retraction, telangiectasia and pain 2 years after irradiation. In the overview of the five-year photographic assessment, no significant difference in worsened breast cosmesis has been observed between the groups at five years after radiation therapy [73]. In trials conducted in crawl position, patients have been treated with moderate or ultra-hypofractionated radiotherapy. Data on acute toxicity have been similar between the schedules while data at 2 years showed a low rate of late toxicities.

The Isocentring Lateral Decubitus (ILD)

By the pioneer experience described by Forquet, the first clinical result by this technique was the reduction of breast thickness as confirmed by CT scans conducted in the first trial. The breast thicknesses measured from skin to skin on a theoretical beam axis was 13 cm on the dorsal position and 7.5 cm on the lateral position; they were 19 and 9 cm at the deepest edge of the field, respectively [45]. This effect had a good impact in reducing the acute toxicity as observed in the following study

conducted at Institute Curie accounting for more than 500 pts treated in LD and with two opposed fields tangent to the chest wall with photons 4–6 MV at SAD 100 cm or 60Co at SAD 80 cm [48]. In the study of Campana et al, a low toxicity rate was reported through a comparative study among the three known breast irradiation techniques using a 60Co unit vs the conventional dorsal decubitus technique (DD) using 4 MV photons or 60 Cobalt vs ILD technique using 5 MV photons. Skin toxicity was assessed using thermo-luminescent dosimeters; the higher skin dose for the lateral field in ILD technique resulted from the bolus effect of the carbon fiber disposer. The median breast thickness measured from skin to skin on the beam axis was 13 cm in the dorsal decubitus position and 6.5 cm in the ILD position (range, 3.5–7.5 cm) [49]. In the study conducted by Kyrova et al on 56 consecutive patients treated with 3D-conformal ILD whole breast RT and conventional fractionation, the first observed effect was the reduction of breast separation measuring between 8 cm and 22.5 cm with an average of 12.25 cm to allow the use of low energy photons. The target coverage was adequate in all patients with a good dose homogeneity. In fact, the maximum dose to the breast was according to the ICRU criteria of 5% and +7%. By this study, 37.5% of patients experienced Grade 1 dermatitis, while in 58.9% Grade 2 dermatitis was recorded and only one patient showed a Grade 3 dermatitis. The cosmetic outcome was good in 76.8% of cases, while a fair outcome was recorded in 3.5% of patients [74]. Also in the set of BC patients with pectus excavatum, the ILD technique allowed to the same breast dose-homogeneity as in the supine technique with a decreased breast thickness by 4.5–6.8 cm. Acute skin toxicity was inconsistent for all patients at completion of ILD radiotherapy [46]. In the study of Bronsart, only patients with large pendulous breasts, pectus excavatum, elderly, heavy smokers to reduce the lung doses and risk of complications as well as the patients with breast conserving surgery after treatment of mediastinal tumors or cardiac disease were treated in ILD. Several fractionation schemes were adopted from conventional to START A and B and weekly five fractions schedules. After a median time of 4 weeks, acute dermatitis was recorded in 93% of the entire cohort. Grade 3 dermatitis was observed in only 2.8% of cases. By multivariate analysis, the cup size and the fractionation schedule had a significant influence ($p = 0.0004$ and $p = 0.0001$ respectively). At 1 year, in 94.1% of cases no skin toxicity, neither cardiac or pulmonary toxicities were reported. The median time to development of fibrosis was 4.6 years. The hypofractionated schedule of 30 Gy in 5 fractions was significantly related to an increased the fibrosis rate ($p = 0.0011$) compared to standard scheme of 50 Gy/25 fr. The cosmetic result was good or excellent for 84.8% of cases at the first evaluation. The risk of breast deformity was also worse in large breast size ($p = 0.02$) [75].

Upright Position

No data are available because the assessment of this position is still under investigation outside clinical trials. However in the experience of Mouhiddin, the patient was treated without interruptions developing a grade 2 hyperpigmentation by week 4 and a Grade 2 inframammary desquamation by week 5 healed with silvadene by week 7. At 6 months follow-up, the breast was soft with normal skin [52].

8.2. Disease Outcomes

In regard to data on local control and survival outcomes in prone position radiotherapy, all the above studies have provided evidences of long-term disease control similar to the supine treatments. In the study of Stengman et al, after a median follow-up of 4.9 years, the 5 year actuarial true local and elsewhere ipsilateral breast tumor recurrence rates were 4.8% and 1.3%, respectively. The 5-year actuarial rates of regional nodal recurrence and distant metastases were 1.6% and 7.4%. Actuarial disease-free, disease-specific, and overall survival rates at 5 years were 89.4%, 97.3%, and 93%, respectively [57]. In the study of Formenti et al, no ipsilateral breast local recurrence, regional nodal recurrence, or contralateral breast cancer were observed, resulting in a 3-year breast cancer-specific survival of 95.6% [58]. Data on long terms outcomes in crawl position are working in progress and are related to a SIB hypofractionated RT in five fractions. However, in the longitudinal analysis of a

phase 2 open-label trial including 100 patients with large breast size randomized between prone and supine positioning, the 5-year overall survival was 96% in both groups [76].

Regarding theILD, overall survival and relapse free interval have been reported by an analysis of Xu et al on 832 consecutive patients. With a median follow-up of 6.4 years, only 36 patients experienced locoregional recurrence and no association with the fractionation regimen was identified ($p = 0.2$). Among these relapsed patients, only 28 pts had “in-breast” local recurrences, two had local recurrences and regional lymph node recurrence and six had regional lymph node recurrence only also in non-irradiated areas. The median time to recurrence was 50 months. Complete mapping of patterns of recurrences was performed and, in most cases, local recurrences were situated adjacent to the primary tumor bed. Multivariate Cox regression analysis showed that the site of recurrence had no significant impact on overall survival ($p = 0.14$) [77]. In up right seated p positioning no data are available.

9. Which Benefit to Organ at Risks ?

Another key point requiring p the adoption of alternative position is to minimize the dose to p the heart, LADCA and ipsilateral lung in left-sided BC patients who are unable to perform DIBH, regardless the breast size. While there is no agreement on an advantage on this topic in trials using free breathing prone position, studies withILD seem to have hit the target very well with a surprising unknown effect like the estimated dose reduction to circulating immune cells (EDIC), which is a new organ at risk to consider. At this moment no dosimetric data are available for up-right seated position.

9.1. Prone

Free or shallow breathing prone position have been hypothesized to be able in reaching this end point in dive and crawl positions as well over the supine position; however, no substantial differences have been recorded and disappointing data have been yielded. In fact, Griem et al found no differences for Heart V30 Gy and V20 Gy ($p = 1.000$) over supine probably due to the anatomical down shift of the lateral and superior border of the heart close to the chest wall [78], as confirmed by Chino’s measurements. In this study, authors calculated 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, discovering a mean 19 mm of systematic displacement in the lateral and superior border of the heart closer to the chest wall in the prone MRI images vs CT scan images acquired in supine position. The mean displacement was 19 mm ($p < 0.001$) with a significant reduction of lung volume between the heart and chest wall in the prone series ($p < 0.001$), thus resulting in no benefit on heart dose [79]. On the contrary, the study of Gregucci et al has reported several a lot of dosimetric advantages for the heart in terms of mean values for MHD = 0.69 Gy, LADCA Dmean = 2.20 Gy, and LADCA Dmax = 4.44 Gy 41 in a comparison with data provided by the current literature on hypofractionated radiotherapy and EQD2 conversion [80]. In the trials conducted in crawl prone positioning, on equal terms of target volume coverages with the supine decubitus, the dose to OARs were significantly lower ($p < 0.05$) for the ipsilateral lung, contralateral lung, thyroid, esophagus. and skin while, again, no significant differences in heart doses were reached [81]. Probably the adoption of DIBH in prone position could had made the difference as emerged by the metanalyses of Lai et al [38]. In this metanalysis, data of 751 patients by 19 observational studies investigating the dose-effect relationship on OAR’s between supine (S-FB) and dive prone in Free breathing (P-FB) and DIBH were collected and analyzed. As a result, compared with the S-FB, the P-FB allowed a significant benefit in dose reducing to heart, left anterior descending coronary artery (LADCA), and ipsilateral lung (ILL) ($p < .00001$), while no significant difference in target coverage between the S-FB and P-FB groups ($p = .66$) were found [38]. Among these studies, the study of Mulliez et al, showed a significant advantage to the heart in S-DIBH, ($p < .001$) while in the P-FB this benefit was significant to LADCA and ILL ($p < .001$) [81]. In another study by Saini et al., the P-FB differences in heart and LADCA dosimetry between the two positions were not confirmed, although a dose reduction to ILL was significant ($P < .001$) [82]. However , in the comparison of P-DIBH and S-DIBH, both studies agreed on th dosimetric

advantage in heart, LADCA, and ILL; ($p < .001$) for P-DIBH over S-DIBH [38]. By a rigid co-registration of a prone positioned patient in SB and DIBH, this matching showed many quantitative volume variations for the organ at risks allowing to a decreased heart volume by 4.3%, in prone DIBH [81].

In a following conformation study on prone SB vs DIBH, in this last technique significantly the mean dose to the heart as in photon and proton plans was decreased. 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 esophagus for photons plan the left lung mean dose decreased by approximately 13%. Meanwhile, in proton DIBH plans, the average mean left lung dose increased by approximately 21%. No significant difference were observed for proton or photon in the mean dose to the contralateral breast [83].

9.2. Isocentring Lateral Decubitus (ILD)

All data collected on patients treated in ILD at Curie Institute are in agreement with the reduction of dose to OAR's at risk as shown in the paper of Campana et al, who reported a reduction dose less 10% of the prescribed dose to the lung and heart due to the beam fitted nearly tangent to the chest wall. Authors concluded that this technique could had been the only solution to irradiate large and pendulous breasts in the meanwhile when IMRT was still under development [49]. Similarly Kyrova et al confirmed this advantage consisting of an average mean ipsilateral 0.96 Gy lung dose, and an average 17.6 Gy maximal dose. Moreover parameters V2 Gy and V5 Gy resulted 9.3% and 0.7%, respectively. In patients with left-sided tumors, very low heart doses were recorded with an average mean heart dose of 1.34 Gy while doses to the contralateral breast and other organs were not relevant [74]. In the study conducted in the series of patients with pectus excavatum, the differences for lung and heart were substantial; in fact in the supine positioning the width of lung and/or heart receiving > 20 Gy ranged between 2.1 cm and 4.3 cm ; on the contrary in ILD , this parameter ranged between 0.5 cm and 1.1 cm ; moreover, while the estimated percentage of ipsilateral lung receiving > 20 Gy ranged from 21% to 34% in the supine technique, this value ranged from 0% to 5% in ILD [46]. This dosimetric advantages seem to involve not only the whole heart but also various cardiac substructures. In fact by a recent comparative study the mean dose to the heart, to the various cardiac structures (left ventricle, left coronary, right coronary), to the homolateral lung, and to the contralateral lung have been significantly lower in isocentric lateral decubitus than in dorsal decubitus. As a result, the average absolute mean dose reductions were -40 cGy for the heart, -27.5 cGy for the left ventricle, -56.5 cGy for the right coronary artery, -64.5 cGy for the left coronary artery, -45.5 cGy for the sinoatrial node, -74 cGy for the homolateral lung, and -4.5 cGy for the contralateral lung. In summary, for all organs at risk, the median dose-volume histograms in the isocentric lateral decubitus were related to lower relative volumes in prone than in dorsal decubitus [84]. Another novelty to take into consideration is the impact of ILD on the estimated dose to circulating immune cells (EDIC). In fact it seems that with this positioning it is possible to induce a potential immune-sparing effect on EDIC by modifying the beam orientation very close to the chest wall in order to reduce the incidental exposure of immune-related structures like heart, lung, liver which contribute to the estimated dose to circulating immune cells (EDIC) [85]. In a retrospective study conducted by Cheptea et al, in ILD, the calculated EDIC value resulted significantly lower than in the supine position (median 0.56 Gy vs. 1.12 Gy; $p < 0.01$). Doses to lung, heart and liver resulted significantly lower. The dose to axilla was reduced, with the mean dose decreasing from 10.2 to 3.8 Gy ($p = 0.016$) and D95% from 0.82 to 0.35 Gy ($p = 0.039$). Authors concluded that these findings may be helpful to preserve immune function, particularly in immunogenic subtypes such as triple-negative breast cancer treated with immune-check point inhibitors [85].

10. Discussion

Supine position is the most common modality applied to deliver adjuvant breast radiotherapy in BC patients worldwide. However not all patients are suitable candidates for this modality because of clinical or anatomical factors which makes troublesome to deliver RT in supine decubitus. The aim of this comprehensive narrative review is to focusing on alternative validated solutions in scenarios in which supine position is difficult to adopt as occurs in post-surgery arm pain, large and pendulous breast, pectus excavatum and left sided breast cancer in order to assure a comfortable RT delivery, improve dose homogeneity to the target and minimize the dose to OAR's. Efforts like the use of higher energy photons, a field-in-field intensity modulation [86], breath-hold protocols have been tested as effective solutions for the majority of BC patients [3]; however, not all BC patients are suitable candidates for these modern techniques in supine decubitus. In addition to arm pain, which is a very limiting factor to maintain this position with the arm above the head, mainly for elderly patients, overweight or obesity are also factors at higher risk of a long-term radiation induced pain [87]. Large or pendulous breasts are a big challenge because of a severe acute skin reactions in the axilla or inframammary fold due to a bolus effect or increased lung dose, particularly in cases where the breast extend laterally beyond the midaxillary line [88]. Acute skin side effects in large and pendulous breast and the following worst cosmetic outcome are expected findings that could be amplified by hot spots leading to double and triple trouble effect in hypofractionated radiotherapy [89], which is the standard fractionation nowadays [90]. Large breast size and heart toxicity in left sided BC patients are closely connected factors. A lot body of evidences have demonstrated the impact of dose to the whole heart in increasing the risk of cardiac events in left sided BC radiotherapy [91]. Large breast size has been found to be related to an increased mean and maximum point heart dose [92] and also the breast's shape [93]. Moreover, the total dose of radiation, young age and the irradiated volume of normal tissue may increase the risk for secondary lung, esophageal, or thyroid cancer, and secondary sarcomas[94-95-96]. Thus, the dose optimization concept to minimize the dose as declared by the acronym **ALARA** should be pursued ever, considering that, compared to the general population, BC patients have an increased risk of secondary non-breast cancers, five or more years after BC diagnosis with and without radiation therapy (RR 1.12; 95% confidence interval [CI] 1.06–1.19) [94]. A novel strategy to overcome these criticisms and deliver adjuvant RT safely, could be the positioning modification over the supine as depicted in this review. The prone positioning and lateral decubitus are both excellent strategies in improving the homogeneity dose distribution into the breast, reducing the breast thickness and avoiding hot spots depositions in the folds with a consequent lower skin toxicity [69,74]. The inframammary fold is completely smoothed in the up-right position by using the specific RT bra; moreover in the up-right it is possible to assure a more comfortable arm position on the flank or above the head while the patient is seated [63]. Crawl prone position offers a better arm comfort and allows to the nodal irradiation with several beams arrangements in IMRT whereas this item is not possible in ILD. In regard to the dose at OAR's, all these positions seem effective in lowering the dose in different ways: in prone position the heart could be spared with DIBH; in ILD the beams arrangements close to the chest are angled to avoid the heart with a consequent advantage on EDIC. In the up- right position, probably the low displacement of organ motion in cranio-caudal direction as found for the intrathoracic organs during a normal breath could exploited the anatomical position of the heart far from the beam. However the set up arrangements in this position need to be well defined. Up to now the best alternative positions are the prone and the ILD. In both modalities specific guidelines have been developed for set up and reproducibility. Further, delineation guidelines have been provided to delineate the breast or chest wall and nodal areas and all the contouring information have been incorporated into an atlas library allowing to an atlas based segmentation (ABS) or in neural network-based autocontouring algorithm to make easy and standardize the target delineation in these novel positions. A summary is provided in Table 1.

Table 1

Topic	Prone	IsoLateral	Up-right
<i>Large and pendolous Breast, pectus excavatum, arm discomfort</i>	allowed; crawl : better arm comfort	allowed	allowed ; RT bra is necessary
<i>RT techniques</i>	2D; 3D conformal; IMRT -VMAT (crawl) with or without DIBH	2D-3D isocentric; no DIBH	On study with protons ; no DIBH
<i>Target</i>	Breast, chest wall nodes in crawl	Only breast	Only breast
<i>Immobilization Devices</i>	Dive and crawl coaches	Techset coach	SBRT table coach; rotating seat gantry free linac and RT bra
<i>Dose inhomogeneity</i>	Reduced hot spots; G2-G3 toxicity low	Reduced thickness breasts Reduced breast separation distance G2-G3 toxicity low	Inframammary fold smooting
<i>Disease control</i>	5 yrs LRR =4.8% 5 yrs OS= 93%-96%	At 6yrs, LRR 4.3% (breast and nodal)	No data
<i>Organ at risk benefits</i>	Heart no differences Advantages in Heart, LADCA, ILL, clBreast ; P-DIBH better	10% reduction dose to Heart, Lung, clBreast EDIC reduced dose	No data

11. Conclusions

Although supine decubitus remains the standard position in WB radiotherapy, alternative solutions to treat patients in particular scenarios not suitable for this modality have been found effective and safe. Prone position and ILD are the most adopted strategies ; up-right is still under investigation to solve several criticisms like the exclusion of the contralateral breast out of the treatments fields, arm immobilization away from the fields with customized arm supports and a stable set up of the trunk. Prone, lateral or up-right position : which one is better ? Regardless of choice, a personalized adjuvant WBI is assured.

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Abbreviations

ALARA = As Low As Reasonably Achievable
APBI = Accelerated Partial Breast Irradiation
BC = Breast Cancer
Co 60 = Cobaltum 60 unit
CT = Computed Tomography
CTV = Clinical Target Volume
2D = Two Dimensional
3D = Three Dimensional
DIBH = Deep Inspiration Breath Hold
EQD2 = Equivalent dose in 2 Gy
ICRU = International Commission on Radiation Units and Measurements
ILL = Ipsilateral Lung
IMRT = Intensity-Modulated Radiation Therapy
IORT = Intraoperative Radiation Therapy
LADCA = Left Anterior Descending Coronary Artery
LENT-SOMA scale = Late Effects on Normal Tissue—Subjective, Objective Management and Analytic scale
Linac = LInear ACcellerator
MHD = Mean Heart Dose
MRI = Magnetic Resonance Imaging
MV = Megavolt
OAR's = Organs at Risk
PE = Pectus excavatum
RILI = Radiation Induced Lung Injury
RT = Radiotherapy
SAD = Source axis distance
SBRT = Stereotactic Body Radiation Therapy
SSD = Source skin distance
V X Gy = Volume receiving xGy
VMAT = Volumetric Modulated Arc Therapy
WBI = Whole Breast Irradiation

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