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Modern Radiotherapy Era in Breast Cancer

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Abstract

Radiation therapy (RT) is one of the major treatment modalities that are used in breast cancer treatment, and depending on the chest-wall anatomy, RT fields have to be customized. Techniques used in planning have been evolving since last two decades from two dimensional (2D) to three-dimensional (3D), while intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and even proton therapy have been an option in daily approach. In addition, technological hardware and software advances in delivery and planning systems, total treatment duration of breast RT have been shortened in last decades along with recent hypofractionated radiotherapy schemes or emerging partial-breast irradiation protocols. The other attractive approach—accelerated partial breast irradiation (APBI) could be a reasonable option for highly selected subpopulation of early-stage breast cancer patients out of a clinical trial. Long-term follow-up results have emerged heart and coronary sparing with maximum safety and efficacy. The most important advance could be named as cardiac sparing—deep breath-hold approach—in all the modern technique improvement. Although most advanced techniques in management of breast cancer have not been verified to increase survival, we suggest recommending resource stratified advanced in order to provide best technical and clinical care in this long-term survivor candidates.

Keywords: radiotherapy, IMRT, VMAT, breath hold

1. Introduction

Radiation therapy (RT) has become an essential component of breast cancer treatment, and depending on the anatomic structure of the region to be irradiated (breast, chest wall or regional lymphatics), RT can be technically challenging and varying from one patient to another.

Breast RT has evolved from two-dimensional (2D) to three-dimensional (3D), while intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and even proton

therapy have been options to discuss with our patients in daily practice. Besides technological hardware and software advances in delivery and planning systems, total treatment duration of breast RT has been changing dramatically in last decades along with recent hypofractionated radiotherapy schemes or emerging partial-breast irradiation protocols. As modern RT allowed us a successive reduction in the treatment-related complications such as fibrosis and long-term cardiac toxicity in addition to improving the locoregional control rates, rationale of as low as possible is appealing to focus more on heart and coronary sparing with four-dimensional (4D) breath-hold techniques. Modern radiotherapy techniques and fundamentals need to be implemented in routine clinical care with maximum safety and efficacy in order to maximize the benefit of locoregional treatment and to minimize the risks of late complications.

We aim to summarize the advances of modern radiotherapy in breast cancer through clinical approaches and routine treatment indications based on present knowledge and evidence-based recommendations.

2. Simulation and immobilization techniques

2.1. Supine

Radiotherapy has been widely used as a part of breast cancer in partial or total mastectomy. Radiotherapy technique can be difficult and variable depending on the anatomy of the patient such as chest-wall concavity, depth of axilla. The first step of radiation treatment is to perform CT simulation to obtain a reproducible detailed anatomy for planning conformal or intensity-modulated radiotherapy with using heart-sparing techniques such as breath hold or heart blocking, especially for left breast cancer patients. Adjuvant therapy for breast cancer starts early 4–6 weeks after surgery or after chemotherapy and was delivered with 6 or 18 MV photons using usually wedged tangent fields, or field and field, 3DCRT and IMRT at 1.8–2.67 cGy doses ranged from 40 to 60 Gy.

Treatment fields are a composite of adjacent whole breast or chest wall, mammaria interna, supraclavicular and axillary fields. The main purpose of the breast radiotherapy fields is to avoid hot and cold dose regions between contiguous fields while minimizing the dose of organs at risk such as lung and heart. RT fields have to be modified according to patient's chest wall and breast anatomy due to its irregular surface, which can cause dose inhomogeneity. At the same time, setup has to be easily applicable and reproducible. Immobilization devices, specially designed for breast cancer treatments, are commercially widely available and are frequently used in daily practice. The best known devices are listed as follows: inclined plane, breast boards, Board-wing butterfly Board, Vac-fix bag-Vacuum Cradle Bed and alpha cradle. The most common, preferred and basic set-up has been performed by a breast board having an inclined plane with an arm support, in supine position. The head of the patient has been pointed to the opposite side, and arm has been abducted (90° – 120°) and externally rotated. Skin folds in supraclavicular field and soft tissue of arm has to be modified if required. The patient is positioned on her back on a stable breast board, and board is angled to ensure the sternum—chest parallel to table. This angle can be adjusted according to clinical needs, but

larger angles can cause increased dose in lungs in patients requiring the supraclavicular field. The border between the chest wall and supraclavicular field is usually placed at the bottom of clavicular head. Radiopaque wires must be used to define incisions and breast borders [1].

Supine positioning has been used for breast cancer patient's alignment for several decades over the world. It provides patient comfort and position reproducibility for the whole treatment period, while ensures better axillary coverage in comparison to prone positioning. When setup errors in supine position were studied with three-dimensional cone-beam computed tomography (CBCT), the average magnitude of error was found to be generally less than 5 mm across a number of studies [2]. Sethi et al. compared both prone and supine positioning for 3DCRT and IMRT plans; traditional three- or four-field planning has inadequate nodal coverage, especially performed in prone setup compared to supine (29 and 42% vs. 50 and 59%), and this disadvantage has been altered by CT-based planning and coverage varied from 92 to 97% depending on IMRT or 3DCRT independent from positioning [3].

2.2. Prone

Rarely, in case of a very large pendulous breast, lateral decubitus or prone position can help. Prone position has been proposed for especially large breasted patient as this volume can cause dose homogeneity due to hot spots and also overlapping breast tissue could create an auto bolus effect, which can abbreviate skin toxicity [4, 5]. While prone setup has also been proposed to increase the lung and heart tissue sparing, the literature has conflicting results in terms of normal tissue dose reduction [6, 7]. Wurschmidt et al. stated that the prone position increasing incidental dose of LAD coronary artery to a mean dose of 33.5 Gy in comparison with supine setup with a mean dose of 25.6 Gy in left whole breast irradiation, without any significant differences in the average mean dose to heart between two different setups [6]. In contrast, Kirby et al. also documented prone positioning to reduce cardiac doses in almost 64% of 30 patients treated whole breast irradiation with a median reduction in LAD mean = 6.2 Gy and 24% of the 30 cases treated with partial breast irradiation (median reduction in LAD max = 29.3 Gy) in addition to reducing ipsilateral-lung (mean) in all whole breast and 61 of 65 partial irradiation cases, and chest wall V (50 Gy) in all whole breast irradiation cases. They concluded that prone positioning is likely to benefit left-breast-affected women of larger breast volume both for whole or partial breast irradiation, and right-breast-affected women regardless of breast volume [7]. Despite the improvement of dose homogeneity, prevention of hot spot regions and lower lung and heart doses, prone position for whole breast irradiation has not been applied in routine clinical practice. Prone setup has been considered to be more problematic to reproduce than supine position and to be less precise. In Varga et al.'s randomized study, the range of displacement was greater in prone position as well as the prone relocation precision presented an expansion over time without any correlation to any patient-related parameters [8]. Patient treatment-related comfort and inadequate target coverage of tumors especially extending down to chest wall were also mentioned as main concerns [9, 10].

Main concern about prone position as setup errors and reproducibility in comparison with the international standard supine position in women undergoing whole-breast radiotherapy was justified by Kirby et al., matching chest wall and clips on cone-beam CT (CBCT) images

acquired prior to the fractions 1, 4, 7, 8, 11 and 14. Setup errors were greater using prone technique than for supine technique as follows: systematic errors: 1.3–1.9 mm (supine) and 3.1–4.3 mm (prone) ($p = 0.02$) and random errors: 2.6–3.2 mm (supine) and 3.8–5.4 mm (prone) ($p = 0.02$). Even patient-comfort-scores and treatment times were similar, calculated CTV-PTV margins were calculated to be larger for prone (12–16 mm) than for supine treatment (10 mm) [11].

2.3. Lateral decubitus position

Lateral decubitus position is a side-lying setup especially generated for large-sized and pendulous breasted patients. In experienced clinics, this setup has been used especially for only breast irradiated cases as lymphatic coverage could be problematic in this position. Campana et al. presented their isocentric lateral decubitus technique at the Institute Curie where almost 500 patients were treated at 50 Gy whole breast radiotherapy [12]. Thin carbon fiber supports and special patient positioning devices have been developed especially for this technique. Their techniques have been proven to show good homogeneity of the dose in breast treatment volume, with extremely low dose to the underlying lung and heart [12]. Despite applicable single center results, this technique has not been spread out and accepted for the routine clinical work flow.

2.4. Thermoplastic bra

Use of thermoplastic bra has been investigated with the objective of minimizing organ at risk doses, as it moves the breast widely lateral. It has been found to provide shallower beam arrangement for left breast (medial: 288°–315° with bra vs. 302°–325° without bra) and to decrease lung doses by 30.6% without any dedicated selection criteria for daily clinical use [13]. The main concern on thermoplastic mask users related with the skin dose and possible associated clinical exacerbation of side effects turned out to be not significant.

3. Planning and delivery methods

3.1. 3DCRT

Conventional two dimensional wedge compensators have been used to shape the treatment fields for many decades. After integration of CT and more sophisticated planning programs in radiotherapy clinical routine, target location can be defined precisely and dose distribution can be obtained more homogeneously. The target and critical structure volumes for three-dimensional conformal radiotherapy (3DCRT) have been defined according to ICRU reports 50 and 62 [14]. A major challenge to improve dose uniformity is the irregular shape and size of the breast while minimizing the risk of treatment-related complications. In recent years, conformal RT, particularly, forward or inverse intensity modulated RT (IMRT), which is a more advanced and sophisticated form of 3DCRT, is becoming popular for breast irradiation as it provides reduced inhomogeneity and/or better normal tissue sparing [15]. Additionally, lately accessible image-guided RT (IGRT) can significantly increase precision of conformal treatment delivery.

3DCRT is based on patient's simulation CT with pertinent anatomical data for target definition as the first and most important step of this advanced planning system. Target delineation

and consistency of target volumes have been accepted as priority, RTOG and EORTC have published breast cancer-specific atlases easily reachable on websites for uniformity among interobservers [16, 17] (<http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx>). In addition to atlas-based contouring publications, quantification of the multi-institutional, multi-observer variability of target and organ-at-risk (OAR) delineation for breast cancer radiotherapy and its dosimetric impacts has been an attractive topic. Li et al. assembled nine radiation oncologists specializing in breast RT from eight institutions to individually delineate lumpectomy cavity, boost planning target volume, breast, supraclavicular, axillary and internal mammary nodes, chest wall and OARs (e.g., heart, lung) on the same CT images of three demonstrative patients with breast cancer [18]. The variability in contouring the targets and OARs was as low as 10% while the volume variations had standard deviations up to 60%. These inter-observer differences can easily end up in significant changes in dosimetry in for breast radiotherapy planning. Further work is warranted to obtain a systematic consensus, especially in the era of IMRT/IGRT, which could be used and easily adapted by the institutions. In similar standardization attempts to minimize the variation in substructure delineation for organs at risk, a detailed cardiac CT atlas have been developed by University of Michigan [19]. If patient has supraclavicular positive lymph node present, additional dose to supraclavicular region will bring into the question of brachial plexus dose. Brachial plexus contouring is mostly thought as a part of head and neck or lung IMRT, so breast radiation oncologists are encouraged to follow contouring guidelines for the brachial plexus (BP) using anatomically validated cadaver data set and head and neck case series [20, 21]. An average margin of 4.7 mm around the anatomically validated brachial plexus contour is instructed to cover and compensate all the anatomic variations of brachial plexus [20].

Many irradiation techniques such as single isocentric 3D conformal whole breast irradiation, prone position technique, four or five field irradiation technique for peripheral lymphatic were described and widely used all over the world and details will not be given as it is not in the scope of this chapter. For each CT data (2–5-mm slices), the dosimetric plans were created by appropriately adjusting the beam apertures such as beam angle, collimator angle, couch angle, wedges, energies, weights and multi-leaf collimators by virtual simulation through digitally reconstructed radiographs (DRR); therefore, the planning goals on coverage and OAR sparing can be achieved. Beam apertures were selected to fully cover the targets for each set of contours. Photon beams of 6 and/or high energy 15–18 MV were used to irradiate breasts, chest wall and boost PTVs tangentially, supraclavicular and axillary nodes. Electron beams with or without a combination of 6 MV photons were used for internal mammary nodes.

As the treatment plan evaluation starts with all axial slices to be checked whether bearing hot or cold regions or not. Next step is the evaluation of dose volume histograms (DVH), which is a graphic expression of dose distribution volume in target or OAR. The planning goals are recommended to cover the breast or chest wall with $\geq 95\%$ with maximal point dose but $\leq 110\%$, while OAR doses are limited with contralateral breast ≤ 3.30 Gy, $\leq 20\%$ of ipsilateral lung $\geq 20\%$, $\leq 5\%$ of heart $\geq 20\%$ for left-sided breast cancer and 0% of heart $\geq 25\%$ for right-sided breast patients, and mean heart dose ≤ 5 Gy [22].

Transition from 2D to 3D has been promising under dosimetric studies revealing an improvement. When conventional 2D and mono-isocentric 3D techniques were dosimetrically compared

in terms of coverage and normal tissue doses, Guillert et al. stated that homogeneity, regional lymphatic irradiation and heart and spinal cord protection were better with the mono-isocentric 3D technique [23]. Leite et al. dosimetrically assessed incidental irradiation of the internal mammary lymph nodes (IMLNs) with using opposed tangential fields with 45–50.4 Gy conventional two-dimensional (2D) or 3DCRT techniques in their cohort of 80 breast cancer patients and documented the mean dose to the IMLNs as 7.93 Gy in the 2D cohort in comparison with 20.64 Gy in the 3D cohort [24]. Even all dosimetric parameters were higher in 3DCRT plans, still we need to improve coverage. These results from the studies analyzed above have proven that more attempts have to be taken to cover target volume without increasing dose to normal organs.

3.2. IMRT

Breast has been one of the complex radiation delivery areas due to the complex anatomical geometry and differences of depth of regional nodal areas. Two-dimensional and 3DCRT have been used safely and with high local control rates, but homogeneity and normal tissue doses have been the two problematic topics until advanced radiation delivery techniques based on image guidance has been established. IMRT can be designed as a forward or inverse planning technique [25]. The forward planning is more common in clinical practice, uses similar beam angles without old school wedges, but manually created field in fields decreasing the hot high dose regions to optimize the dose distribution [26, 27]. Forward planning follows optimization algorithms to provide dose homogeneity and coverage [27].

The use of IMRT in breast cancer radiotherapy has been investigated in couple of fundamental prospective clinical studies [28, 29]. First was the Royal Marsden study comparing 2D wedge based, 3D and IMRT techniques in terms of acute and long-term side effects. The primary end point was objective change in breast appearance based on serial photographs of 306 patients obtained before treatment, at 1-, 2- and 5-year follow-up. The conventional treatment arm patients were 1.7 times more likely to have a change in breast appearance compared to IMRT arm patients, suggesting that minimization of dose inhomogeneity in the breast reduces late adverse effects, whereas there were no significant differences on the patient reported breast discomfort and quality of life between 2SD and IMRT arms [28]. Second randomized trial by the Canadian group has supported the findings and concluded that 4–7 segmented IMRT decreased moist desquamation rates which was also related with the breast cup size [30]. Third prospective trial from Cambridge has focused selective forward IMRT planning on the patients if inhomogeneity exceeds 107% with standard planning and concluded that improved plan parameters with forward IMRT were obtained [29]. Dosimetrically reduction in surface doses using IMRT technique has been shown to be almost 20%, and this has been turned to be a reduction in skin acute side effects from 52 to 39% in clinical experience without compromising local regional control success [26]. All pertinent studies have supported the value of early breast cancer treatment with IMRT providing lesser acute skin toxicities, which would effect long-term cosmetics [31, 32].

The next question was whether more homogenous dose distribution will turn into survival advantage compared to conventional 2D or 3DCRT. Yang et al. retrospectively reviewed 234

patients treated for stage 0–III breast cancer (conventional:131 vs. IMRT: 103) and documented locoregional failure-free survival and disease-free survival at 8 years as 96.7 vs. 97.6% and 91.2 vs. 93.1% for conventional RT and IMRT, respectively [33], while less frequent acute skin toxicity by IMRT did not translate into a significant decrease in late toxicity rates in follow-up.

IMRT can add benefit when hypofractionation is prescribed. Hardee et al. compared toxicity of patients treated according to the Canadian hypofractionation regimen (40 patients with 3DCRT and 57 with IMRT) [34] and demonstrated IMRT reducing the maximum dose (Dmax median, 109.96% for 3DCRT vs. 107.28% for IMRT; $p < 0.0001$) and improving median dose homogeneity in comparison with 3D-CRT. Besides, grade 2 dermatitis decreased from 13% in the 3DCRT group to 2% in the IMRT group, and decreasing rates of acute pruritus and grade 2–3 sub-acute hyperpigmentation were noted in IMRT group [34].

The use of more sophisticated treatment techniques will be more critical especially for organ at risk—lung and heart—doses in more complex treatment fields for locally advanced breast cancer patients. A dosimetric study by Lohr et al. evaluated the effect of IMRT on cardiac doses compared to 3DCRT at their CT data set of 14 patients [35]. Plans were generated by two conformal beam angles chosen to minimize heart and lung doses for 3DCRT and nine beams (0° – 335° , 25° apart) over left hemi-thorax in a coplanar fashion for IMRT [35], where IMRT had provided superior dosimetric parameters for maximal dose to heart, V30 and V40 of heart and left ventricle except mean and median dose of heart which increased from 6.8 to 8.5 Gy and from 1.02 to 2.77 Gy, respectively. In the light of these results, Lohr et al. stated that mean risk of excess cardiac mortality significantly decreased from 6.03 to 0.25% according to their relative seriality model [35].

Conventional irradiation of regional nodal irradiation was known to deliver inadequate homogeneity and to be usually a challenge depending on the patients' geometry, location close to the normal organs and patient-dependent variation of depth [3, 36]. In a dosimetric study, three field, four field, CT-based 3D and forward IMRT treatment options were compared and superior nodal coverage has been achieved by both CT-based 3D and IMRT techniques, despite the fact that contralateral breast and ipsilateral lung V5 and V20 doses increased by 3–4 field IMRT [3]. The recent rotational form of IMRT, volumetric arc therapy, has also been studied dosimetrically for locally advanced breast cancer patients requiring regional lymph node irradiation with conflicting results [37, 38]. Ma et al. replanned left-sided, locally advanced patients with 3DCRT-field in field, five field IMRT (2 tangents, 2 anterior and 1 supraclavicular field) and two coplanar partial arc VMAT to a prescription dose of 50 Gy [37], the planning goals were defined as follows: PTV:[D95 (95% of PTV receiving a prescription dose or higher) = 50 Gy, V47.5 Gy $\geq 95\%$, V53.5 Gy $\leq 5\%$]; heart: [Dmean ≤ 10 Gy, V10Gy $\leq 20\%$, V20Gy $\leq 15\%$]; left lung: [Dmean ≤ 15 Gy, V10Gy $\leq 30\%$, V20Gy $\leq 20\%$, V30Gy $\leq 10\%$]; right breast:[Dmax ≤ 3 Gy]; spinal cord: [Dmax ≤ 45 Gy]; left humeral head: [Dmean ≤ 50 Gy]. Both 5F-IMRT and 2P-VMAT plans demonstrated comparable PTV coverage (V95%), hotspot areas (V110%) and conformity (all $p > 0.05$) which were significantly superior to 3DCRT-FinF, and 5F-IMRT plans provided significantly less heart and left lung dose than 2P-VMAT (all $p < 0.05$); therefore, Ma et al. specified that 5F-IMRT has dosimetrical advantages compared with the other two techniques in comprehensive breast irradiation for

left-sided breast cancer based on balance between PTV coverage and normal organ sparing [37]. Tyran et al. evaluated arc therapy and a forward-planned multi-segment technique with a mono-isocenter technique for left-sided breast treatment, involving lymph node irradiation including the internal mammary chain [38]. VMAT improved PTV coverage and dose homogeneity but distributed low doses to a larger volume which blurred the clinical benefits. In another preclinic study revealed that VMAT achieved similar PTV coverage and sparing of organs at risk, with fewer monitor units and shorter delivery time than cIMRT with conventional modified wide-tangent (MWT) techniques for locoregional radiotherapy of breast cancer [39]. Based on the conflicting dosimetric studies and without any published clinical study, no general recommendations for VMAT could be drawn for its use in daily clinical practice, leaving the decision to the institutional decision based on the planner's experience, expectations and required quality assurance.

Especially forward IMRT, using tangential beam angles and creating multiple segment, can be accepted as standard approach in clinical practice taking into the considerations of acute toxicity [40, 41]. The published literature of forward or inverse IMRT use in clinical practice of breast cancer, has mainly focusing on toxicities and have short follow-up time. In Canadian guidelines, based on the similar local control and overall survival results, IMRT has not been recommended over tangential radiotherapy field design [42]. Of course, the cost of using new technologies needs to be considered as if they only reduce toxicity profile due to treatment. In USA, systematic analysis of Medicare reimbursement data during 2012–2015, for prostate, anal, gynecological and head-neck cancers, declared that IMRT has been more costly than 3DCRT approximately 12.834\$ per patients and this cost can go up to 19.113\$ and breast IMRT has been named as the least expensive IMRT depending on the less complex structure compared to a head and neck workload [43].

3.3. Tomotherapy

Lately, an innovative method of IMRT has been developed as a combination of helical IMRT with CT image guidance at the University of Wisconsin-Madison named as TomoTherapy® Hi•Art® [44]. A small megavoltage X-ray source was built in an analogous to that of a CT X-ray source, and the geometry provided the chance to deliver treatment applying the 360° rotation of the CT gantry and the couch moving the patient slowly through the center of the ring, with the mounted megavoltage linear accelerator around the gantry ring in a spiral fashion to direct the beam at a slightly different plane at the each rotation of gantry. TomoTherapy Hi•Art can also accomplish a quick CT scan before each treatment starts for image guidance in the era of modern linear accelerators [45].

TomoTherapy has been used to treat other sites than breast such as prostate, brain, head and neck, lung, prostate, etc. [44], and when considered for breast cancer treatment, the format of helical tomotherapy sound unsuitable based on the use of all gantry angles delivering low doses to areas such as contralateral lung and breast in comparison with conventional standard tangents field design which would only deliver a scatter dose to these organs. Starting point of clinical experience of helical tomotherapy for breast cancer has been a treatment of complicated case scenarios such as bilateral breast cancer to be irradiated for the bilateral breasts/ chest wall and regional nodes. Kaidar-Person et al. reviewed nine-cases treated for breast and

regional nodal irradiation with Helical tomotherapy in their institute in 5 years of period [46]. The average lung V20, lung V5 and heart mean dose was 29%, 66% and 20 G, respectively. Clinical significant acute toxicity was observed such as dysphagia (5/9), fatigue (4/9), nausea and weight loss (1/9) and skin desquamation (9/9) [46]. Goddu et al. also estimated the practicability of using helical tomotherapy for locally advanced left-sided breast cancer in a dosimetric planning study on 10 CT data sets comparing a multifield three-dimensional technique with the tomotherapy treatment planning for 50.4 Gy dose [47] and found tomotherapy to increase the minimal dose to the planning target volume and improve the dose homogeneity. While decreasing the mean percentage of the left lung volume receiving 20 Gy in the tomotherapy plans decreased from 32.6% to $17.6 \pm 3.5\%$, while increasing lower dose levels as V5 from 25 to 46%. The same observation was present for heart such tomotherapy decreased V35 Gy from 5.6 to 2.2% with an increase from 7.5 to 12.2 Gy for mean heart dose levels [47]. These dosimetric studies confirmed that tomotherapy plans provided better dose conformity and homogeneity than three-dimensional radiotherapy, while the disadvantage of tomotherapy seems to be low dose bath and higher lower dose parameters for the normal tissue bearing an unpredictable effect for the long-term effects. In a case presentation from Institut Curie, comparison of 3DCRT dorsal decubitus and 3DCRT lateral isocentric decubitus with tomotherapy plan for T2N0M0 breast cancer patient revealed that tomotherapy plan has been preferred as it could deliver optimal coverage to the planning target volumes while also providing tolerable doses to the patient's heart and lungs [48].

The use of the tomotherapy unit in fixed gantry positions with the beam intensity modulated by the micro collimators as the patient is moved through a stationary gantry could be the best approach in breast cancer treatment. This design can limit the low dose bath effect and created an almost a tangential approach. This form of tomotherapy has been used by O'Donnell and they present their case solutions for bilateral disease, left breast irradiation, pectus excavatum, prominent contralateral prosthesis and internal mammary chain disease [49]. Their planning results with a more limited number and angle of beams than standard helical tomotherapy technique results reassured better conformity of treatment with improved coverage of the planning target volume, including regional nodes, without field junction problems [49].

The major two important concerns in tomotherapy similar to IMRT and VMAT are time-consuming planning and quality assurance than standard breast irradiation and increasing low dose 'bath' as a major concern on late oncogenesis. Published comparative studies of conformal radiotherapy and IMRT have revealed generally better target volume coverage and organ-at-risk dose reductions and worse risk of secondary cancer induction based on increased out-of-field leakage radiation with higher number of fields and used monitor units in IMRT plans; the overall estimation of lifetime attributable risk of the radiation-induced cancer risk was lower with 3DCRT than with IMRT or VMAT [50, 51]. Comparison of five treatment modalities including tomotherapy, 3D conformal radiotherapy, field in field, IMRT and VMAT in breast cancer patients, tomotherapy plans provided better dose homogeneity in the target volume, as IMRT and VMAT plans created better dose coverage and dose conformity; the V20Gy of the ipsilateral lung was the lowest in the single isocentric IMRT plan, followed by the 3–4 arc VMAT, 3D-CRT, TOMO, and Field in field plans, and the V10Gy was the highest

for the VMAT plan among the five modalities [52]. Keeping in mind that lifetime attributable risk of secondary cancers depends on organ's distance from the primary beam and the used modality, risk of secondary malignancies expected in the ipsilateral lung, thyroid, contralateral lung and contralateral breast were found to be the highest for the VMAT plans, followed by the IMRT plans [34], and remarkably, the risk of the Tomotherapy was comparable to or lower than those of the 3DCRT and Field in field plans [52]. This study clarified one of the major concerns of tomotherapy and can reflect more common use of tomotherapy in breast cancer treatment.

3.4. Proton therapy

Proton radiation is a particle radiation which has a capability of depositing therapeutic radiation at a fixed point with sparing of tissues beyond the target. Although proton therapy is prescribed in fractions similar to photons, its radiobiological effect rate is higher than (1.1) photons [53]. The use of protons in treatment has been evaluated primarily for tumors requiring high doses or located in close proximity to critical structures such as prostate cancer, brain tumors and childhood cancer. Despite dosimetric advantages, extensive cost of equipment and maintenance has been defined as an important barrier fact for protons to become widespread in clinical use. Nowadays, 61 centers are operating over the world, and in 2020, the estimated number of proportional proton radiotherapy centers will be 91 [54]. Clinically, proton has limited use in breast cancer, although it has an exclusive capability to archive full coverage of the breast or chest wall with a rapid fall-off of dose beyond the target which would be a great contribution for acute and late cardiopulmonary toxicities. Hence, greater data were present for accelerated partial breast irradiation (APBI) with longer follow-up.

Galland-Girodet et al. compared photon-based and proton-based APBI in phase 1 study and 7 year ipsilateral breast recurrence rate 11 vs. 4%, respectively. The physician assessment of overall cosmesis was good or excellent for 62% of proton patients, compared with 94% for photon patients depending on more skin toxicities such as telangiectasia, pigmentation changes, fibrosis and patchy atrophy [55]. Loma Linda Medical center has the largest proton-based APBI experience including 100 patients treated with 40 Gy (RBE) in 10 daily fractions, with patient and physician reported cosmesis, tumor recurrence and dermatitis rates of 90, 3 and 62% at 5 years, respectively [56]. Proton-based APBI, therefore, is accepted as a non-inferior treatment option for early-stage breast cancer patients.

There are few single-center case series that presented the use of proton for treating peripheral lymphatics, especially for locally advanced breast cancer with short follow-up periods. In a dosimetric comparison of proton in combination with 3DCRT to 3DCRT (photon + electron) and IMRT, proton have improved coverage and has decreased dose exposure to normal tissue adjacent to target [57]. First clinical report from Massachusetts General Hospital consists for 12 locally advanced breast cancer and they based their prospective trial on a dosimetric comparison of 11 patients plans with protons, partially wide tangent photon fields (PWTF) and photon/electron (P/E) fields. Proton therapy achieved superior coverage with a more homogeneous plan compared to PWTF and P/E fields, also considerable cardiac and pulmonary sparing was achieved with proton therapy as compared to PWTF and P/E [58]. They afterwards

reported feasibility of proton delivery of post-mastectomy proton radiation to a dose of 50.4 Gy [relative biological effectiveness (RBE)] to the chest wall and 45–50.4 Gy (RBE) to the regional lymphatics with or without reconstruction. With maximum grade 2 skin toxicity (75%) and no radiation pneumonitis reported, proton RT for post-mastectomy RT was found to be feasible and well-tolerated. They noted that mean heart dose was as low as 0.44 Gy and this was the strongest argument for using protons for extensive chest-wall irradiation.

The second report by Memorial Sloan Kettering, including 30 patients, supported the positive results of early toxicity and normal tissue sparing shown by the previous literature [59]. They have used uniform scanning beams with anterior orientation for delivery. Supraclavicular field and chest-wall field were matched anteriorly, a set of beams with same orientation has been shifted 1-cm superior/inferiorly for feathering to minimize hot spots. Similar to previous report, mean heart dose was 1 Gy (RBE) and grade 2 skin toxicity rate was 71.4%, also 29% of the patient experienced moist desquamation [59]. Uniform scanning proton therapy provides 100% dose at the skin without using a bolus for post-mastectomy patients. This effect depends on the technique, selective skin sparing can be obtained by pencil beam scanning with proximal range modulation advantage.

University of Florida recently published a prospective pilot study including 18 women (stage IIA–IIIB, 10 patients with proton therapy, 8 patients with proton-photon combination) requiring comprehensive breast radiation [60]. Proton therapy was shown to improve target coverage for the internal mammary nodes and level 2 axilla while median cardiac V5 was 0.6% with PT and 16.3% with conventional radiation ($p < 0.0001$). Within median 20-month follow-up, only grade 3 toxicity developed was dermatitis in four patients (22%) [60].

The most important advantage of proton treatment was almost none ‘low dose bath’ dose compared to IMRT techniques as high integral doses of heart, lung and coronary arteries could be associated with increased long-term complications and secondary cancers for especially young population. This philosophy behind using proton therapy in breast cancer treatment has been an attractive research area.

Another repeatedly cited concern concerning about the use of proton radiation is cost. Although the dosimetry serves for advantage dose distribution and superior normal organ sparing compared to standard RT, clearly more long-term and superior clinical results are also warranted to rationalize the higher cost of proton therapy. Lundkvist et al., accomplished a cost analysis demonstrating that proton therapy could be cost-effective if main aim is primarily heart sparing [61]. As a conclusion, proton radiotherapy dose distribution of radiation to chest wall/breast and regional lymphatics has been proven to provide excellent coverage with improved sparing of adjacent normal structures but until the cost of proton therapy decreases, we have to select eligible patients carefully.

3.5. Hypofractionation

Conventionally, radiation treatment after breast surgery has prescribed to the whole breast with total doses of 45–50 Gy delivered in 1.8- to 2-Gy daily fractions, and in many cases followed by an additional 10- to 15-Gy boost dose to the tumor bed, for a total of 5–6 weeks of

daily treatment. The cost and travel distance to radiotherapy centers for multiple weeks are the most known barriers to the administration of radiotherapy. One of the solution was using increased daily fractions to lessen the total treatment time. Radiobiologic studies have proposed that breast cancer cells have a alpha-beta ratio which is similar to late reacting normal irradiated tissues [62] and the Royal Marsden Hospital/Gloucestershire Oncology Center trial based on the alpha-beta ratio of almost 4 Gy aiming equivalent tumor control with shorter hypofractionated schedules to a lower total dose randomized 1410 women with invasive breast cancer to receive 50 Gy radiotherapy given in 25 fractions, 39 Gy given in 13 fractions, or 42.9 Gy given in 13 fractions, all given over 5 weeks [63, 64]. After a median follow-up of 9.7 years, the risk of ipsilateral tumor relapse after 10 years was 12.1% in the 50 Gy group, 14.8% in the 39 Gy group, and 9.6% in the 42.9 Gy group [64]. Hypofractionation schemes were confirmed to be safe, effective and encouraged shorter course for early-stage breast cancer patients without compromising local recurrence or survival end points.

Hypofractionated regimens of irradiation to the whole breast have been studied by Canadian and English radiation oncology groups. Initially, Canadian trial enrolled 1234 women with invasive, lymph node-negative breast cancer treated by lumpectomy with negative pathologic margins and small to moderate breast size (breast separation ≤ 25 cm) to randomize to receive hypofractionated whole breast irradiation of 42.5 Gy in 16 fractions over 22 days versus standard whole breast irradiation of 50 Gy in 25 fractions over 35 days [65]. Acute toxicity was recorded similar between the arms, with only grade 2 or 3 radiation skin toxicity observed in 3% of patients in each arm. Additionally, long-term outcomes also were comparable between treatment schemas, the 10-year risk of local recurrence was 6.2% in the hypofractionated arm and 6.7% in the standard arm, as well as the rate of good or excellent cosmesis was 69.8% in the hypofractionated arm and 71.3% in the standard arm [65]. The following supporting hypofractionation randomized trial presented by START Trialists' Group-START-A enrolled 1410 patients to either standard fractionated whole breast irradiation or hypofractionated schedules of 42.9 or 39 Gy in 13 fractions over 5 weeks [66, 67]. Disease-free survival and overall survival were found to be similar in all arms except more moderate or marked skin toxicities were recorded at 39 Gy such as breast induration, telangiectasia and breast edema [66, 67]. The START B trial randomized 50 Gy in 25 fractions over 5 weeks versus 40 Gy in 15 fractions over 3 weeks in 2215 women (pT1-3a pN0-1 M0), and after a median follow-up of 6.0 years, reported lower local-regional tumor relapse (2.2 vs. 3.3%) and also lower rates of late adverse effects by photographic and patient assessments at 5 years in the accelerated hypofractionated arm [68]. Combining these START trials have suggested that use of 40 Gy in 15 fractions schema with fewer fractions of larger dose per fraction is at least as safe and effective as the historical standard regimen (50 Gy in 25 fractions) for women after primary surgery for early breast cancer [68].

An unplanned subgroup analysis of Ontario study proposed that the hypofractionated regimen was less effective in patients with high-grade tumors, having 10 years of cumulative recurrence incidence of 4.7% for standard RT and 15.6% for the hypofractionated RT with high-grade tumors [65]. In contrast, START A and B studies did not demonstrate a significant outcome measure respective to grade [67]. The proportion of patients with high grade tumors were 19, 28% and 23% in the Canadian, START A and START B trials implying insufficient numbers

for appropriate conclusions as well as not calculated for a proper hypothesis. Therefore, the American Society for Radiation Oncology (ASTRO) task force could not reach a strict conclusion for comfortably advising use of HF-WBI for women with high-grade tumors until other studies clarified the outcome [69]. Bane et al. reexamined molecular and pathological features of 989 patients whose tumor blocks were present and checked thoroughly the association between tumor classifications and local recurrence rates [70]. The 10-year cumulative incidence was 4.5% for luminal A and basal-like, 7.9% for luminal B and 16.9% for HER-2 enriched tumors ($p < 0.01$); albeit tumor grade, molecular subtype or hypoxia did not predict any correlation between local recurrence and hypofractionation. Accordingly, hypofractionated radiotherapy is now considered appropriate regimens as a first treatment option for all grades and molecular subtypes of breast cancer; ASTRO published an evidence-based guideline for the use of hypofractionation and whom to prescribe in clinical practice [69]. Mainly, the routine suitable group for hypofractionation was defined as follows: age older than 50 years, stage T1–T2, no use of chemotherapy and central axis dose of 93–107%. The recommended schedules were 42.5 Gy in 16 fractions (Canadian trial), 41.6 Gy in 16 fractions over 5 weeks (START A), 40 Gy in 15 fractions over 3 weeks (START B). As the clinical approach spread all over the radiation oncology world, the suitable group criteria's expanded and nowadays this scheme is suitable for all ductal carcinoma in situ or T1–T2 invasive ductal carcinoma tumors with N0 status above 40-year old without any restriction. In case of regional lymph node irradiation, the literature has low toxicity rates in retrospective analysis regarding brachial plexopathy with the use of hypofractionation.

There is an increasing attention to more intensified hypofractionation in the treatment of breast cancer which has ground for randomized UK FAST Trial, published in 2001 with first results [71]. They have compared 50 Gy in 25 fractions, 30 Gy in 5 fractions or 28.5 Gy in 5 fractions, all over 5 weeks, and based on adverse effects in the breast with 3-year median follow-up, 28.5 Gy in 5 fractions was found to be comparable to 50 Gy in 25 fractions and was significantly better than ultra-short schema 30 Gy in 5 fractions [71]. Further studies are ongoing to build upon these findings including questions for assessing the values of concomitant boost with IMRT.

3.6. Accelerated partial breast radiotherapy

The role of partial breast irradiation (PBI) has been based on the knowledge that whole breast radiotherapy does not appear to prevent the development of new primary cancer in elsewhere localization in breast other than primary tumor quadrant being true recurrences. Pathological studies have examined specimens, and it revealed that residual tumor is detected in 15 mm or less in more than 90% of the cases [72]. PBI is the limited volume irradiation of breast tissue covering just around the tumor bed with a margin. PBI delivers a larger fraction dose in shorter total treatment time to reduce RT waiting period. Today, this technique can be applied by either intracavitary brachytherapy or MammoSite, interstitial brachytherapy, intra-operative techniques using electrons or X-rays at 50 kVp or external beam radiotherapy.

In order to select proper patients for these modalities, three different groups have been described where only minor differences were present between the set criteria's. American

Society of Therapeutic Radiation Oncology (ASTRO) recommendations are divided into three categories labeled as 'suitable' [≥ 60 years, tumor size ≤ 2 cm, pN0(i+/i-), no LVSI, invasive ductal carcinoma (IDC), margin (-), unifocal], 'cautionary' [50–59 years old, tumor size 2.1–3.0 cm, limited/focal LVSI, invasive lobular carcinoma (ILC), close margin (< 2 mm), unifocal, DCIS ≤ 3 cm] 'unsuitable' [≤ 50 years, tumor size ≥ 3 cm, DCIS ≥ 3 cm, positive margin, multifocal, LVSI (+), \geq pN1] groups. American Society of Breast Surgeons (ASBS) has defined as age 45-year old or older for invasive cancer, age 50 years or older for DCIS, invasive carcinoma or ductal carcinoma in situ, Total tumor size less than or equal to 3 cm in size, negative microscopic surgical margins, pN0 [73]. American Brachytherapy Society (ABS) APBI criteria's based on a review of clinical and pathologic factors by the clinician [age (≥ 50 years old), tumor size (≤ 3 cm), all invasive subtypes and ductal carcinoma in situ, surgical margins (negative), LVSI (not present) and nodal status (negative)] [74]. To clarify the patient selecting for APBI depending on the clinicopathological features, a nomogram detecting the locoregional recurrence in patients treated with accelerated partial-breast irradiation has been developed. The nomogram was established on the results of a total of 2000 breasts (1990 women) treated with APBI at William Beaumont Hospital (n = 551) and in the American Society of Breast Surgeons MammoSite Registry Trial (n = 1449). Almost all APBI types were prescribed (multiplanar interstitial catheters, 98; balloon-based brachytherapy, 1689; and three-dimensional conformal radiation therapy, 213). Univariate analysis found that age < 50 years, pre-/perimenopausal status, close/positive margins, estrogen receptor negativity and high grade were associated with a higher frequency of LRR [75].

Interstitial brachytherapy is the first technique used to treat only a partial amount of breast tissue. At that time, electron beam therapy was not available, so boosts were delivered to tumor bed using low dose rate (LDR) interstitial brachytherapy. With the advent of high-energy linear accelerators, electron beam boosts for the most part replaced interstitial brachytherapy with better dose homogeneity and improved overall cosmesis parallel to the experience [76]. To date, numerous single-arm and some randomized studies have been published examining multi-catheter interstitial brachytherapy [77–80]. Commonly, these studies registered patients with early-stage low-risk invasive and in situ carcinoma of, T1 or T2, with some allowing up to three positive axillary lymph nodes (N1) with negative surgical margins. Interstitial catheters were placed with a free-hand technique or a breast template with the placed surgical clips between 4 and 8 weeks after surgery. Earlier studies tend to use LDR or pulsed dose rate (PDR) sources, but the majority of the more recent series have been using ^{192}Ir high dose rate (HDR) brachytherapy. Generally, the target volume has been defined as the tumor bed plus 1–2 cm, 45–50 Gy with LDR and 30–36 Gy (using twice daily fractionation) with HDR. Local recurrence rates were ranged from 0 to 8.9% [77, 79–81]. Usually, the rates of recurrence were low except the Guy's Hospital experience which stated an ipsilateral breast tumor recurrence rate of 18% [82]. GEC-ESTRO published 5-year follow-up results of randomized trial comparing interstitial brachytherapy to whole breast radiotherapy for patients aged 40 years or more, small T1-2N0-miM0 (less than 3 cm) with negative margins and no lympho-vascular invasion (LVI) and excluded women with multifocal tumors. This trial has been conducted in 16 different centers in Europe. Planning and dose limits were as follows: The maximum skin dose less than 70% of the prescribed dose, the dose nonuniformity ratio

(V100/V150) below 0.35, 100% of the prescribed dose covered at least 90% of the target volume (coverage index ≥ 0.9). APBI was delivered a total dose of 32.0 Gy in eight fractions (8×4.0 Gy) or 30.3 Gy in seven fractions (7×4.3 Gy), with fractionation twice a day, was used for HDR brachytherapy. A total dose of 50 Gy with pulses of 0.60–60.80 Gy/h (one pulse per h, 24 h/day) was given by PDR brachytherapy. Analysis of 1184 patients with low-risk invasive and ductal carcinoma in situ treated with breast-conserving surgery has demonstrated that the cumulative incidence of local recurrence was 1.44% with APBI and 0.92% with whole-breast irradiation. The five-year risk of grade 2–3 late side-effects to the skin was 3.2% with APBI versus 5.7% with whole-breast irradiation, and grade 3 fibrosis at 5 years was noted as 0.2% with whole-breast irradiation and 0% with APBI. Polgar et al., randomized 258 pT1N0-1miM0, grade 1 or 2; T1N0-N1miM0, grade 1 or 2 patients with invasive breast cancer (unifocal tumors, tumor size less than 20 mm, clinically or pathologically N0, or single microscopic nodal metastasis) after wide local excision of tumor and negative pathological margins (greater than 2 mm and less than 2.0 mm) to receive either 50 Gy whole-breast irradiation ($n = 130$), APBI with multi-catheter HDR brachytherapy ($n = 88$), or APBI with electron beam irradiation ($n = 40$). The local recurrence at 10 years was 5.9% after APBI and 5.1% with whole-breast irradiation ($p = 0.767$) after median follow-up of 10.2 years. Excellent-to-good cosmetic results were 81% with APBI and 63% with whole-breast irradiation ($p < 0.01$) [77]. The literature has confirming results showing that the overall cosmesis scores were good to excellent for the majority of the patients with low rates of late complications [77, 80, 83]. Recently, phase 2 study of NRG Oncology/Radiation Therapy Oncology Group 9517 published 10-year rates of oncological outcome measures of accelerated partial breast irradiation using multi-catheter brachytherapy including 98 stage I/II unifocal breast cancer patients (tumor size < 3 cm, negative surgical margins and 0–3 positive axillary nodes without extracapsular extension). High dose rate group received 34 Gy in 10 twice-daily fractions over 5 days and low dose rate (LDR) brachytherapy had 45 Gy in 3.5–5 days. Only five regional recurrences were defined. The 10-year disease-free survival, overall survival and contralateral breast event rates were 69.8, 78.0 and 4.2%, respectively [84]. Despite the encouraging results of the literature and long years' experience, interstitial brachytherapy stayed limited to selected institutes owing to the requirements of dedicated team, experience, skills and specific equipment.

External-beam XRT is the other option for APBI administration with an advantage of non-invasive nature, widespread availability of required resources, and knowledge of final pathology before the treatment planning. External APBI is most frequently administered in a 38.5-Gy regimen divided into 10 fractions given twice per day for 5 days. Rodríguez et al. reported on the 5-year outcomes of 102 patients with features of pT1-2pN0M0 invasive ductal carcinoma, tumor size 3 cm or less, negative margins and grade 1 or 2 histology randomized to receive whole breast irradiation (48 Gy/with or without boost) using three-dimensional conformal external beam radiation therapy (37.5 Gy in 3.75 Gy per fraction) or APBI [85]. Beam weights were manually optimized to cover the PTV by the 95% isodose line while maintaining a hot spot of $< 105\%$. For imaging, portal images of each beam and an orthogonal (anteroposterior) images were obtained for the first and second fractions. At a median 5 years of follow-up, aside from no local recurrences, APBI also reduced acute side effects and radiation doses to healthy tissues compared with WBI. Physician assessment showed that $> 75\%$ of patients in

the APBI arm had excellent or good cosmesis similar to whole breast group, and these outcomes has not changed at the follow-up [85].

An interim analysis of the RAPID (randomized trial of APBI) trial was important in terms of cosmetic results in which 1108 patients (invasive ductal carcinoma or ductal carcinoma in situ with tumors <3 cm, negative margins and no involved axillary nodes) were randomized to either 3D external beam APBI or WBRT. RAPID trial used 3DCRT in 38.5 Gy/10 fractions over 5–8 days (with a minimum 6 h gap between fractions given on the same day) and two fractionation schemas for WBRT: 50 Gy/25 fractions or 42.5 Gy/16 fractions. Baseline post-treatment nurse assessment for adverse cosmesis was 19% in the APBI arm and 17% in the WBRT arm and at the third year evaluation, these rates were increased in APBI arm to 29% and remains stable –17% for WBRT [86]. The worsening cosmetic results have been shown previously reported by single institute reports of Michigan University and Tufts University. Despite the good cosmetic outcome results in the non-randomized, multicenter studies, external beam-based APBI has been used with caution in practice [87–90]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 trial that randomized 3000 patients to WBXRT or partial breast irradiation (PBI) finished patient recruiting but will be completed at April 2020. As most of the patients on the non-WBXRT arm have received 3D-CRT, the results will help to enlighten the cosmetic results and routine use of external beam as an option [91].

Catheter-based radiation therapy (brachytherapy) has been performed with MammoSite™ (Hologic, Marlborough, MA, USA) as the first balloon-based catheter and following with single and multi-lumen catheters Contura®, and SAVI™, in historical order. These catheters can be found in different sizes and shapes. All placement for insertion shared the same protocols where placement can be performed at either at the time of lumpectomy or as a postponed procedure up to 2–6 weeks after operation. Ultrasound guidance is the key device to detect the seroma and guide the catheter insertion along the longest axis diameter of the cavity. The device can be inserted through the surgical scar or a separate incision pathway could be chosen depending on Ultrasound guidance or the cavity evaluation CT of the patients that was obtained at radiation oncology clinic before placement. This cavity evaluation CT also serves for detecting proper size of the catheter. If the APBI decision was already given before surgery, a ‘placer’ can be put in the cavity and the balloon placer is then inflated with sterile saline to a diameter of 4.0–5.0 as it is described above and after evaluating the final pathology, it can be replaced by the selected size of the catheter. After insertion, a new CT scan is then obtained to assess the conformance of the balloon to the cavity and the presence of air or fluid gaps. A ratio of air or fluid in the cavity to balloon surface of less than 10% is usually acceptable, and also just for single lumen catheters a balloon-skin distance equal or greater than 5 mm is warranted. The lumpectomy cavity is then delineated and expanded by 1 cm to define the PTV. The most commonly prescribed dose is 3.4 Gy BID to a total of 34 Gy. Recommended dose constraints and contouring recommendations are given in **Table 1**. It is recommended that the placement and the position of the catheter has to be checked before each treatment.

MammoSite is the first developed balloon-based single-lumen device and major disadvantage is the minimum distance of skin required from skin to cavity which is about 7 mm. After

new developments, MammoSite also changed its single lumen form and a multi-lumen catheter released similar to Contura and SAVI.

Contura™ (SenoRx, Inc. Aliso Viejo, CA, USA) is a similar balloon catheter that has multiple catheters within the balloon and also comes in different sizes to fit the cavity. The multiple catheters offer optimization of the plan to that better normal tissue and skin sparing meaning that skin cavity distance has no more importance for patient selection, allow more precise

Contouring

-Excision cavity

Outlined based on either *visualization* on CT, or if placed, contouring around the surgical clips

Clinical target volume CTV)

CTV = Excision cavity + 15 mm

CTV limited to 5 mm *from the skin surface* and by the *posterior breast tissue* (chest wall and pectoralis muscles are not to be included)

PTV

PTV = CTV + 10 mm

PTV is used to generate the beam aperture with an additional margin for penumbra

PTV_EVAL

PTV_EVAL = PTV — anything outside the ipsilateral breast, the first 5 mm of tissue under the skin (in order to remove most of the buildup region), and any PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscle, and lung)

Normal tissue

Skin

Thyroid
 Ipsilateral lung
 Contralateral lung
 Heart

Dose volume histogram
 Acceptable criteria's:

-Dose volume histogram analysis of target coverage will confirm $\geq 90\%$ of the prescribed dose covering $\geq 90\%$ of the PTV_EVAL

-The actual volume of tissue receiving 150% (V150) and 200% (V200) of the prescribed dose will be limited to ≤ 70 cc and ≤ 20 cc, respectively.

-Critical normal tissue DVHs within 5% specified value (uninvolved normal breast: ideally, $< 60\%$ of the whole breast reference volume should receive $\geq 50\%$ of the prescribed dose.)

-Dose delivered twice a day for a total of 10 treatments over a period of 5–10 days

Unacceptable:

-Dose volume analysis of the target volume confirms <90% of the prescribed dose and/or <90% coverage of the PTV_EVAL

-Critical normal structure DVH exceeds 5% of the specified value (uninvolved normal breast: ideally, <60% of the whole breast reference volume uninvolved normal breast: ideally, <60% of the whole breast reference volume should receive $\geq 50\%$ of the prescribed dose and <35% of the whole breast reference volume should receive the prescribed dose)

Normal tissue

- **Contralateral breast:** The contralateral breast reference volume, contoured using the same methods described for the ipsilateral breast reference volume, should receive <3% of the prescribed dose to any point
- **Ipsilateral lung:** <15% of the lung can receive 30% of the prescribed dose
- **Contralateral lung:** <15% of the lung can receive 5% of the prescribed dose
- **Heart (right-sided lesions):** <5% of the heart should receive 5% of the prescribed dose
- **Heart (left-sided lesions):** The volume of the heart receiving 5% of the prescribed dose (V5) should be less than the 40%
- **Thyroid:** maximum point dose of 3% of the prescribed dose. Should receive $\geq 50\%$ of the prescribed dose.)
- The maximum skin dose at any point is $\leq 145\%$ of prescription dose, assuring that the skin dose does not exceed acceptable limits the maximum allowable skin dose is kept below 100% of the prescription. If the balloon-skin distance is 5–7 mm, up to 145% of the prescribed dose is also acceptable

Table 1. Recommendations for APBI contouring and DVH evaluation based on RTOG NSABP PROTOCOL B-39 [91].

treatment planning. The other advantage of this catheter is the vacuum ports which helps to remove fluid and air if needed.

The SAVI™ (Cianna Medical, Inc., Aliso Viejo, CA, USA) device has also multi-catheter (6, 8 or 10) body in an elliptical shape. The catheter body of the device does not have a balloon around the catheters and can be opened and closed like an umbrella which helps fit easily the fat tissue of the cavity. As it locked in the lumpectomy cavity, the rotation and the problems with the delivery will be ruled out. ClearPath™ (Renata Medical, Irvine, CA, USA) is a single entry multi-catheter device which allows both HDR- and LDR-based APBI treatment. If the patient carries Ir125 seeds placed in ClearPath device, they have to wear a fully

shielded bra during the low dose rate APBI treatment. Axxent® (Sunnyvale, CA, USA) is a novel electronic brachytherapy system that is developed to simplify the brachytherapy technique. In its form, there is an iridium seed-based single catheter balloon, also it does not require a high dose rate afterloader unit or a shielded vault and can be turned on and off such that it can be used in the office setting [92]. The balloon is radiolucent to improve visibility on breast radiographs and CT images. In a dosimetric evaluation, electronic brachytherapy plans were stated as providing comparable target coverage, increased high-dose regions, and a significantly reduced dose to the ipsilateral breast and lungs as well as the heart compared with the iridium-192 treatment plans [93]. Also, the intersocietal Electronic Xoft Intersocietal Brachytherapy Trial (EXIBT) registry recruited 400 patients and at 1-year follow-up demonstrated that breast infection occurred in two (2.9%) patients, and no tumor recurrences were reported. Cosmetic outcomes were excellent or good in 83.9–100% of evaluable patients at 1, 6 months and 1 year [94].

The MammoSite Registry of the American Society of Breast Surgeons has the biggest number of patients with this device with a median follow of 63.1 months. The registry data had 1449 patients with a five-year actuarial IBTR rate is 3.8% and axillary recurrence rate is 0.6%. Excellent/good cosmetic results at 60, 72 and 84 months were as follows: 91.3, 90.5 and 90.6%. The overall rates of fat necrosis, symptomatic seroma and infections remained low at 2.5, 13.4 and 9.6% with few late toxicity events beyond 2 years. These results have been found to be comparable to the rates for whole breast irradiation and other forms of APBI. Mann et al. retrospectively examined the long-term results of 111 patients treated with MammoSite APBI and revealed that the incidence of ipsilateral breast tumor recurrence was 2.7%. The incidence of ipsilateral axilla nodal recurrence was low as well (1.8%). Excellent to good cosmesis rate was 98.1% of the patients. The cosmetic results were found to be paralleled to the mean value of maximum skin dose: excellent, good and fair cosmesis were 88.9, 92.7 and 109.5% of the prescription dose, respectively [95]. These results also confirmed by Northwest University prospective MammoSite study (n:33), which noted that local recurrence is 100%, and cosmetic results were good to excellent in 94% of the patients [96]. Gitt et al. used MammoSite brachytherapy as a boost (15 Gy in 2.5-Gy fractions) after whole breast radiotherapy for carefully selected early-stage pT1-2, pN0-1, M0 disease 107 patients were treated with breast-conserving therapy and adjuvant radiotherapy with MammoSite followed by WBI (median = 50.4 Gy). In a short follow-up period of 21 months, no ipsilateral breast-tumor recurrences have been observed with an acceptable toxicity profile of 28% asymptomatic and 10% symptomatic seroma in 90 days after treatment [97]. Another retrospective long-term single institute (N:157) results confirmed that rate of ipsilateral breast recurrence was low as 2.5% at a median follow-up time of 5.5 years (range 0–10.0 years). Good to excellent cosmetic outcomes were achieved in 93.4% of patients and proved that skin dose >100% significantly projected the development of telangiectasia (50 vs. 14%, $p < 0.0001$) [98].

In Mayo clinic, a prospective protocol for completing all locoregional treatment (surgery and APBI) within 10 days with acceptable complication rates and cosmesis. Intraoperative multi-lumen strut-based device was placed for 123 women [age 50 years or older with clinical T1 estrogen receptor positive (ER+) sentinel lymph node (SLN)-negative invasive ductal cancer or pure ductal carcinoma in situ]. Analyzing the procedure, 110 (90%) of these patient

underwent intraoperative catheter placement, whereas 13 did not due to intraoperative pathology findings. Prescribed radiotherapy was completed within 5 days at 109 APBI patients (99%), for all patients, this duration was 9 days with 6% 30-day complication rate. The local recurrence rate was 1.8% (two patients), and excellent or good cosmesis was achieved in 88% of patients [99]. Evaluating early toxicity in a prospective manner in 132 patients treated with strut-adjusted volume implant (SAVI) for early-stage breast cancer, SAVI has been observed as a safe treatment option with one acute and three late skin infections (two were grade 3), besides grade 1 or 2 late toxicities of hyperpigmentation (44%), telangiectasia (0.8%), seroma (9%), fat necrosis (5%), and fibrosis (12%). Crude local recurrence rate was 4% at a median follow-up time of 20 months [100]. It has to be noted that the literature studying new catheters except MammoSite are mostly presenting early results for feasibility and toxicity profile. Wobb et al. recently documented late side effects of 1034 patients treated with brachytherapy-based APBI (interstitial 40%, applicator-based 60%) and whole breast irradiation using intensity modulated radiotherapy [101], and stated that though brachytherapy-based APBI was associated with higher rates of \geq grade 2 seroma formation (14.4 vs. 2.9%, $p < 0.001$), telangiectasia (12.3 vs. 2.1%, $p = 0.002$) and symptomatic fat necrosis (10.2 vs. 3.6%, $p < 0.001$), there was no difference between rates of fair or poor cosmesis [101].

The use of partial irradiation in the treatment of ductal carcinoma in situ was tested in a prospective multicenter trial consisting 41 patients (42 breasts) with the eligibility criteria's of a diagnosis of DCIS confirmed by core needle biopsy, unicentric disease ≤ 3 cm in size by mammogram, and an estimated life expectancy of >5 years [102], where the mean tumor size was 0.82 cm with comedo necrosis in 21.4%, and estrogen receptor positivity was 52.4%. Abbott et al. documented four patients (9.8%) developing an IBTR (all DCIS) outside the treatment field with a 3.2 years mean time of recurrence, and the actuarial recurrence rate at 5 years of 11.3%. It has to be noted that all patients with recurrence had at least one normal mammogram after treatment and before recurrence. Even all the recurrences were DCIS and occurred outside of the treatment field, prospective randomized trials have to wait before recommending routine use of APBI for DCIS [102].

In a meta-analysis of nine randomized trials comparing APBI vs. whole breast radiotherapy, the overall mortality was 4.9% and as no difference was observed in the proportion of breast cancer-related deaths, both non-breast cancer mortality with a difference of 1.1% ($p = 0.023$) and total mortality with a difference of 1.3% ($p = 0.05$) were found to be significantly lower in PBI than WBI cohorts which encourages PBI in selected patients with a 25% reduction in five-year non-breast cancer and overall mortality in comparison with WBI [103]. The most criticized study in APBI practice was the population-based retrospective analyses by Smith et al. based on Medicare billing codes rather than actual clinical outcomes defining the rate of mastectomy after APBI or whole breast radiotherapy [104], which analyzed 6952 breast cancer patients treated with brachytherapy and 85,783 with whole breast radiotherapy over 67-year old. Mastectomy was required in more women treated with brachytherapy (3.95%) than WBI (2.18%), and though five-year overall survival was similar on both group 87.66% with brachytherapy vs. 87.04% WBI, brachytherapy was shown to be linked with more frequent infectious (16.20 vs. 10.33%) and noninfectious (16.25 vs. 9.00%) postoperative complications such as breast pain (14.55 vs. 11.92%), fat necrosis (8.26 vs. 4.05%) and rib fracture (4.53 vs. 3.62%; $p \leq$

0.01 for all) [104]. These rates contradicted with the ones by Wobb et al. with mastectomy rates due to local recurrence (3.1% for WBI-IMRT and 1.2% for APBI, $p = 0.06$), or other reasons (0.8 and 0.6%, $p = 0.60$) [101]. In another series by Mann et al., the salvage mastectomy rate was 2.7% for patient treated with APBI which is not as high in Medicare data [95]. Although single institute results favored APBI, Medicare-based data slowed down the use of APBI which nowadays is recommended mainly in prospective protocols.

Intraoperative radiotherapy is the delivery of a single fraction of radiotherapy at the time of surgery directed to only tumor cavity. This can help to reduce long treatment duration for patient; but in today's practice, it is still expensive due to additional staffing, workload and specific equipment requirements. The available methods of delivering IORT are low-energy X-ray systems, electron beam radiation therapy and high dose rate afterloaders.

The Intrabeam® device (Carl Zeiss, Oberkochen, Germany) is a low-energy X-ray IORT device that has solid and rounded applicators in different sizes. After the lumpectomy is performed, Tungsten-impregnated sheets are used to shield the wound, and afterwards, applicator fixing in the tumor cavity is placed. A 20-Gy one-time dose is delivered at the surface of the applicator decreasing to a dose of 5 Gy at a depth of 1 cm from the cavity. Treatment time varies from 20 to 40 min. Shielding is essential to reduce radiation scatter, operation room walls will often provide sufficient shielding for the low-energy X-rays but measure environmental radiation dose rates around the theatre is essential.

There are three commercially available mobile linear accelerators, which can deliver electron beam radiation therapy the Novac7® (Hitesys S.p.A., Aprilia, Latina, Italy), the Liac® (Sordina, Padova, Italy) and the Mobetron® (IntraOP Medical Inc, Sunnyvale, CA USA). Both Novac7® and Liac® have been used in a phase-III trial, the ELIOT trial. The irradiation procedure is easily completed in 2 min, and the delivered dose is 21 Gy with the depth of 90% isodose ranging from 13 (3 MeV) to 24 mm (9 MeV). The breast tissue is mobilized over a lead/aluminum shield placed posteriorly to protect the chest wall and viscera. By means of these systems are delivering electrons, non-shielded operating rooms can be used but the team has to leave the operation room while the radiation is delivered.

High dose rate (HDR) afterloader (Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY, USA) within a dedicated shielded operating facility (Brachytherapy Unit) was assessed by Memorial Sloan-Kettering Cancer Centre. Treatment is delivered with HDR to the tumor bed using an iridium 192 (¹⁹²Ir) source connected to a quadrangular silastic template applicator named Harrison-Anderson-Mick (H.A.M.®). A dose of 18 Gy was used as a standard approach. At 5 years (median follow-up 68 months), local recurrence of 7% reported by this techniques but has a limited use due to the high cost and the need of special shielded operating room.

Several single institution studies have been present in the literature on the feasibility and effectiveness of IORT, but only two phase-III trials have been published, the targeted intraoperative radiotherapy-alone (TARGIT-A) trial and the electron intraoperative treatment (ELIOT) trial with results at a medium follow-up of 2.4 and 5.8 years, respectively. TARGIT-A is an international cohort of 3451 patients who were randomized to either whole

breast radiotherapy (40 to 56 Gy \pm 10 to 16 Gy boost) or Intrabeam®, with a single 20 Gy fraction prescribed to the surface of the applicator. All clinical T1–T2 \leq 3.5 cm, N0–1 invasive breast cancer patients were eligible if they were aged 45 years or older and suitable for wide local excision for invasive ductal carcinoma that was unifocal on conventional examination and imaging [105]. After the pathological evaluation, if the patients had adverse pathologic features including LCIS, lymphovascular space invasion, positive nodal status or other parameters defined at each center, postoperative WBI was added, and the APBI was counted as the boost. At a median follow-up of 2 years and 5 months, local recurrence rate was 3.3% in the APBI group and 1.3% in the WBI group ($p = 0.04$). Interestingly, even though cases were selected carefully, local recurrence in patients treated with TARGIT as a second invasive procedure by reopening the wound ($n = 1143$) was 5.4% and higher than with EBRT (1.7%). The difference was explained as a possibility of a delay in wound fluid suppression of tumor cells, a delay of radiation or a geometric miss when inserting the applicator postsurgery by authors [106], and “postpathology” TARGIT by reopening the wound was not recommended. Furthermore, OS or distant metastases, the rates were similar with low skin toxicity profile. There was no difference in hematomas needing surgical aspiration, seromas needing greater than three aspirations, infections requiring intravenous antibiotics or surgical intervention or skin breakdown or delayed healing rates between APBI and WBRT [105].

The ELIOT trial also uses intraoperative electrons as a single dose of 21 Gy prescribed to the 90% depth compared 50 Gy of external beam radiation therapy in which 1305 patients presented with tumors 2.5 cm or smaller and 48 years or older. After tumor excision, the breast tissue was mobilized and a lead/aluminum shield was placed to protect chest wall and underlying structures. The breast tissue as a target was rearranged over the shield. An appropriately sized collimator (4–8 cm) was inserted. At a median follow-up of 5.8 years, the 5-year recurrence rate was 4.4% for ELIOT versus 0.4% for the EBRT. For low risk women the 5-year IBTR was 1.7%. For patients with one or more high risk features (tumor size, receptor status, nodal positivity and grade), the 5-year IBTR was 11.8% for the 178 women (30.4%) with 1 or more risk factors versus 1.7% for the 407 ELIOT low risk women (69.6%) [107]. The rate of ELIOT patients who could be defined as ASTRO suitable subgroup was 23%, and ipsilateral breast recurrences ratio for them was 1.5% at 5 years and alike to whole breast group. ELIOT study results revealed low rates of skin and pulmonary damage [108]. There was no difference in terms of pain, retraction or fibrosis. Overall survival was the same between the two arms. The applicator sizes used in the ELIOT trial are not specified, but it has been advised that to guarantee uniform coverage of microscopic residual disease, the IOERT applicator dimension size has to be chosen at least 1.5 to 2 cm larger than the maximum tumor dimension [109]. Although the above IO-APBI trials show some promising early results, the follow-up for ELIOT is short especially given that breast cancer can recur many years later.

Cochrane meta-analysis including all types of APBI has been published in 2016 consisting seven randomized trials studying 7586 women of the 8955 enrolled [110]. Local recurrence-free survival decreased from HR-1.62 to HR-1.11 for women receiving PBI/APBI compared to WBRT, in addition to poorer physician-reported cosmesis with PBI/APBI. Oncological outcomes as cause-specific, distant metastasis-free, relapse-free survival or mastectomy rates

were not affected by this small local recurrence difference, besides no difference in overall survival with PBI/APBI. As acute toxicities seem to be reduced by partial irradiation, this effect did not lead into an advantage for late term subcutaneous fibrosis. 'Elsewhere primaries' (new primaries in the ipsilateral breast) found to be more frequent with PBI/APBI. This meta-analysis cannot help to determine which technique increased the local recurrence or elsewhere primary detection. Ongoing trial will address the questions in future [110]. Despite small differences in local control, the advantages of the patients with APBI such as short treatment duration or easy application during surgery can increase patient treatment compliance. IO-APBI could be a reasonable option for highly selected subpopulation of early-stage breast cancer patients out of a clinical trial.

3.7. Breath hold-cardiac sparing methods

Breast cancer radiotherapy reduces the risk of cancer recurrence and death demonstrated by randomized trials, but as radiation delivery requires tangential and selectively mammaria interna fields, meta-analyses also have found an increase in cardiac deaths following breast cancer radiotherapy associated with the volume of the heart receiving 5 Gy or more [111]. Decreased myocardial function or coronary artery diseases are the most common cardiotoxicity besides less common toxicities of myocardial infarction, congestive heart failure, pericarditis, arrhythmias, angina or valve dysfunction [112]. Darby et al. steered a population-based case-control study of major coronary events in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark. The overall average of the mean doses to the whole heart was 4.9 Gy (range 0.03–27.72), and the rates of major coronary events were associated with a 7% increase in risk of ischemic events per gray increase in mean heart dose with no apparent threshold. This effect of radiation on heart was increasing within the first 5 years after radiotherapy and found to be unrelated to the presence of cardiac risk factors at the time of radiotherapy.

Due to the interplay between respiratory motion and MLC motion during IMRT delivery, the planned and expected doses could be different. Respiratory motion is a well-known factor during treatment planning for breast IMRT, dosimetric studies presented that PTV dose heterogeneity increases as respiratory motion grows. The lung and heart doses also change with respiratory motion. As a result, a larger margin is proposed from CTV to PTV margin [113]. The breath-hold technique could help to minimize the effect of potential negative dosimetric impact arising from interplay effect of multileaf collimator and breathing motion during delivery of IMRT [114, 115].

In clinical practice, there are two commercially available devices: active breathing coordinator™ (ABC_DIBH) (Elekta, Crawley, UK) and Varian RPM system guiding patients to hold their breath while radiotherapy is delivered, which pushes the heart down and away from the radiotherapy field. Even the benefits of these systems were proved by dosimetric studies, they are not used more widespread as it was used in only 19% of EORTC centers in 2010 and just 4% of UK centers [116, 117]. This could be due to additional cost, education of staff and time-consuming procedure depending on patient's capacity and therapist's experience.

In the early 2000s, the Real-time Position Management (RPM) system from Varian Medical System (Palo Alto, USA) consisting of two reflectors attached to an external marker-cube placed on the patient's abdomen was released. The motion of the cube marker, reflecting the breathing pattern of the patient, is evaluated by software that controls the scanner, based on predefined criteria [118]. The advantage of this RPM system is the constant monitorization of patient respiration, and a beam-hold condition automatically occurs if the breath-hold level departs from the planned one [119]. The patient can easily track their performance on screen, also reproducibility is the other important advantage of this system.

The ABC method was established at William Beaumont Hospital and is currently commercialized by Elekta, Inc. as the active breathing coordinator. Also the VMAX Spectra 20C (VIASYS Healthcare Inc, Yorba Linda, CA, USA) and the SpiroDyn'RX (Dyn'R, Muret, France) which are working in the similar principles [120]. The ABC apparatus can be used to suspend breathing at any predetermined position along the normal breathing cycle, or at active inspiration. A digital spirometer is used measure the respiratory cycle, which is connected to a balloon valve. In an ABC procedure, the patient breathes normally through the apparatus. When an operator "activates" the system, the lung volume and the phase (i.e., inhalation or exhalation) at which the balloon valve will be closed are specified. The patient is then instructed to proceed to reach the specified lung volume, typically after taking two preparatory breaths. At this point, the valve is inflated with an air compressor for a predefined duration of time, thereby "holding" the patient's breath [120].

There is solid evidence from retrospective and dosimetric planning studies, demonstrating reduction in dose to the heart and coronary arteries with deep inspiration breath-hold treatment of left-sided breast cancers for both early and locally advanced breast cancer therapy with regional irradiation. In a dosimetric analysis, free and breath-hold technique were planned with both forward and inverse IMRT showing a significant reduction in radiation exposure to the contralateral breast, left and right ventricles, as well as proximal and especially distal LAD by breath hold with forward IMRT, as inverse IMRT provided no additional advantage [121]. For whole breast radiotherapy, Wang et al. reported a reduction in mean heart dose from 3.2 Gy forward-planned IMRT in free-breathing to 1.3 Gy for forward-planned IMRT in breath hold. Another confirming study, recruiting 319 breast cancer patients revealed that deep inspiration breath-hold plans expressed large reductions in dose to the heart compared with left-sided FB plans; V20Gy of the heart is reduced from 7.8 to 2.3%, V40Gy from 3.4 to 0.3% and mean dose from 5.2 to 2.7 Gy (-48%, $p < 0.0001$) while median target coverage is slightly improved [122].

In William Beaumont Hospital experience revealed that moderate deep inspiration breath hold achieved using an active breathing control (ABC) device, compared with free breathing (FB) during treatment with deep tangents fields (DT) for locoregional (LR) irradiation of 15 breast cancer patients, reduced the heart V30 for 6 of the 9 left breast patients, entirely avoiding heart irradiation in 2 of these 6 patients and the mean percentage of both lungs receiving more than 20 Gy from 20.4 to 15.2% [123]. Twenty centers in order to compare clinical aspects of respiratory-gated conformal radiotherapy during breast cancer irradiation versus conventional conformal radiotherapy and reassured the feasibility and good reproducibility of the respiratory gating systems with the reduction in the dose delivered to the

heart during irradiation of the left breast [119]. Even locoregional irradiation is considered, breath-hold technique still added benefit with breath-hold technique significantly by reducing Dmean Heart and Dmean LAD compared to free breathing for both the whole breast and chest wall and regional irradiation groups. When Dmean Heart of <4 Gy had been set as a criteria for planning, all the plans in whole breast radiotherapy has been met this apart from breathing pattern, but only five of nine patients (56%) in the comprehensive breast irradiation group were able to meet this constraint with free breathing, compared to all patients with deep breath hold was in compliance with the criteria of Dmean Heart <4 Gy [124]. Addition to the routine use of deep breath old techniques for left breast cancer patients, Essen et al. recommend it to use for right breast also. The gain for locoregional breast treatment without IMN, the average mean lung dose reduced from 6.5 to 5.4 Gy for the total lung and from 11.2 to 9.7 Gy for the ipsilateral lung while if internal mammaria lymph node irradiation is added significant gain will continue for lung doses, which can translate into a lower risk of pneumonitis and secondary lung cancer rates in future [125]. As a summary of the published literature, deep breath hold reduced the mean heart dose by up to 3.4 Gy when compared to a free breathing approach. Also deep breath-hold technique was announced as stable and reproducible on a daily basis [126].

Breath-hold technique's dosimetric benefits have been clearly in the literature, but these techniques are not yet in widespread use. The reasons for this could be explained by this technique needs commercially available solutions necessitate specialist equipment. Another breath-hold technique described as 'voluntary breath-hold technique' described. This breath-holding technique monitories breath-hold consistency using the distance moved by the anterior and lateral reference marks away from the treatment room lasers in breath hold to monitor constancy at CT-planning and treatment setup. Light fields are then visually checked breath-hold consistency before and during treatment. This technique is announced as simple and inexpensive, but still there is concerns about the reproducibility and consistency [127]. A randomized study conducted at the Royal Marsden Hospital (Sutton, UK), The UK HeartSpare Study, has confirmed that interfraction reproducibility with the voluntary breath-hold technique is analogous to the performed with the spirometry-based device. Addition to this, voluntary technique offers a time advantage at planning-CT and treatment setup and is preferred by patients and radiographers alike compared to using the spirometry-based device [128]. In HeartSpare II study, the VBH technique is currently being ongoing at 10 UK radiotherapy centers to confirm that the technique is applicable in a multicenter setting where presented preliminary data suggest multicenter application of VBH is found to be both actual and practicable at heart-sparing [129].

According to Royal Marsden Hospital protocol firstly patient's asked to practice at home holding their breath, while lying down, initially for 5 s, and building up in 5 s intervals to 20 s. During the standard CT simulation procedure, position of crosses in free breathing and while taking a deep breath in marked on the patient. The duration of the breath hold has to be noted. All the details and a video related to this technique has been published by Barnett et al. [127]. Systematic and random error range for each beam and in each plane reported as 1.5–1.8 mm and 1.7–2.5 mm, respectively [127].

As a conclusion, to date, there is only retrospective or dosimetric studies were presented and no data studying the clinical benefits and oncological outcomes for patients treated with this technique. Especially, the cardiac data will be presented in 15–20 years. Under these circumstances, the clinical application of deep breath-hold technique is important and advisable. In our clinic, we routinely train all our left breast cancer patients and use RPM system during the simulation and treatment to provide the consistency and reproducibility of breath-holding period. After forward IMRT planning, DVH are evaluated according to criteria's as follows: Spinal cord Max <45 Gy or Max <36 Gy (if >2.5 Gy/Fx), heart V20 <4%, V10 <15%, total lung V20 <35%. Our aim is to reduce mean heart dose as low as possible. Average mean heart doses were usually under 4–5 Gy and 2.5 Gy for left-sided RT and right-sided RT including IM nodes. After adding segments, the 105% isodose line cloud should not been seen except in the corners due to lung transmission.

4. Conclusion

Modern radiotherapy techniques have been evolving in the last two decades. Supine positioning will be continued to be used for breast cancer simulation for several decades over the world as it provides patient comfort and position reproducibility for the whole treatment period, while in rare indications such as a very large pendulous breast or depending on institution choice lateral decubitus or prone position can help. The reflection of modern techniques such as three-dimensional (3D), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) has been evolving in breast therapy. Even dosimetric studies has demonstrated more homogenous dose distribution and normal organ sparing, still survival data, and the long-term effects of normal tissue sparing on survival will be answered in future. Especially, forward IMRT, using tangential beam angles and creating multiple segment, can be used in clinical practice taking into the considerations of acute toxicity but using tangential radiotherapy field design is still acceptable. There is an increasing attention to hypofractionation in the treatment of breast cancer, while there are still unanswered questions in regional lymph node and expander irradiation. Another attractive approach—APBI could be a reasonable option for highly selected subpopulation of early-stage breast cancer patients out of a clinical trial. Results of ongoing trial comparing APBI techniques to external radiotherapy will address the future of APBI techniques as a routine clinical approach. The most important advance could be named as cardiac sparing-deep breath-hold approach in all the modern technique improvement. Retrospective or dosimetric studies were presented the benefit of using commercially available techniques or voluntary performance, while clinical outcomes could be presented in 15–20 years. Under these circumstances, the clinical application of deep breath-hold technique is important and advisable.

Although most advanced techniques in management of breast cancer have not been proved to increase survival, we suggest recommending resource stratified advanced techniques to be decided institutionally in order to provide best technical and clinical care in this long-term survivor candidates.

Abbreviations

RT	Radiation therapy
2D	Two-dimensional
3D	Three-dimensional
IMRT	Intensity-modulated radiotherapy
VMAT	Volumetric modulated arc therapy
4D	Four-dimensional
CT	Computed tomography
CBCT	Cone-beam computed tomography
3DCRT	Three-dimensional conformal radiotherapy
ICRU	International Commission on Radiation Units and Measurements
IGRT	Image-guided RT
RTOG	Radiation Therapy Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
OAR	Organ-at-risk
DVH	Dose volume histograms
IMLNs	Internal mammary lymph nodes
ASTRO	American Society for Radiation Oncology
LDR	Low dose rate
PDR	Pulsed dose rate
HDR	High dose rate
APBI	Accelerated partial breast irradiation
DCIS	Ductal carcinoma in situ
PBI	Partial breast irradiation
Dmean	Mean dose

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