review

Target motion management in breast cancer radiation therapy

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Background. Over the last two decades, breast cancer remains the main cause of cancer deaths in women. To treat this type of cancer, radiation therapy (RT) has proved to be efficient. RT for breast cancer is, however, challenged by intrafractional motion caused by respiration. The problem is more severe for the left-sided breast cancer due to the proximity to the heart as an organ-at-risk. While particle therapy results in superior dose characteristics than conventional RT, due to the physics of particle interactions in the body, particle therapy is more sensitive to target motion.

Conclusions. This review highlights current and emerging strategies for the management of intrafractional target motion in breast cancer treatment with an emphasis on particle therapy, as a modern RT technique. There are major challenges associated with transferring real-time motion monitoring technologies from photon to particles beams. Surface imaging would be the dominant imaging modality for real-time intrafractional motion monitoring for breast cancer. The magnetic resonance imaging (MRI) guidance and ultra high dose rate (FLASH)-RT seem to be state-of-the-art approaches to deal with 4D RT for breast cancer.

Key words: breast cancer; target motion; particle therapy; intrafractional movement

Introduction

Breast cancer is the second most common cancer worldwide.[1-4] Radiation therapy (RT) is proved to be efficient for breast cancer treatment.[5-7] Breast cancer RT is mainly categorized into whole-breast irradiation (WBI) and partial-breast irradiation (PBI), each consisting of a variety of techniques.[6,8] Although the principal goal of breast cancer RT is to damage tumor while sparing normal tissues, superior treatment outcome is hampered by some uncertainties such as organ motion. Target motion imposes a negative impact on breast cancer RT, particularly for the left-sided breast. Organ motion is generally categorized into three types: (1) patient motion, (2) interfractional motion occurring between the fractions, and (3) intrafractional motion referring to all involuntary movements during a treatment fraction. Examples of the latter include respiration cycle, heart beating, muscle relaxation/tension, bowel, and rectal/bladder filling. As the intrafractional motion follows approximately a systemic pattern in an intrafractional motion always increases the apparent size of the target resulting in a larger irradiated volume. It, in turn, increases secondary cancer risk, as well. Owing to the importance of breast cancer, several techniques are introduced to address the problem of respiratory-induced target movement.[9] It should be also noted that for the right-sided breast cancer, the manage-

ment of target motion is not regular mainly due to the larger distance between the heart and the target compared to the left-sided cases. In contrast to lung RT, few studies are focusing on tumor motion management in breast RT. In addition, the literature about addressing breast tumor motion in particle therapy is also sparse. The problem is more challenging in particle therapy than conventional RT mainly due to stricter accuracy requirements and thus mandates special considerations.[10] It should also be noted that this review covers only the external-beam RT techniques for breast cancer. To this end, this literature review aims at providing an overview of current intrafractional target motion management techniques for breast cancer irradiation, highlighting the gaps, and finally presenting future directions in the field of interest.

Literature search strategy

To conduct a comprehensive literature review, all English full-text records indexed in both Scopus and/or PubMed were searched and considered. The published year was limited between 1990 and 2021 to ensure the inclusion of all recent publications. The following keywords were used: "intrafraction", "intra-fraction", "intrafractional", "intra-fractional", "breast cancer", "radiotherapy", "radiation therapy", "proton therapy", "proton beam therapy", "motion", "particle therapy", "and respiration","prone", or "supine". Four identification, screening, eligibility, and inclusion steps were then followed. The selection criteria were as follows: (1) monitoring intrafractional target motion in breast cancer treatment and (2) irradiating moving target in breast cancer treatment. However, some identified articles were excluded since they were either duplicated or irrelevant. Of them, 106 articles fulfilled the inclusion criteria. No specific additional filter was applied. Moreover, additional 45 original articles, reviews, and books were also considered as they were applicable to breast cancer and/or they provided general information on target motion monitoring and management techniques in RT.

The nature and extent of target motion in breast cancer

Breast subjects to intrafractional movement caused by both baseline shift and respiration and therefore breast cancer RT is always challenged by target motion.[6] Usually, the amount of breast motion ranges from 1 mm to more than 20 mm displacement in some cases.[6,11-15] Moreover, studies reported that this motion tends to be non-linear (*i.e.*, it peruses semi-circles rather than a straight line) for many tumors.[16] Most of the tumors (~78%) in the breast move with less than 10 mm peak-to-peak displacement.[16] Smith *et al*. showed the maximum range of intrafractional variation of central lung distance (CLD), as the best predictor of setup uncertainties, for any patient on the day, is 2.5 mm. Maximum changes of lung and heart area during treatment are 270 mm^2 and 360 mm^2, respectively.[17] Saliou *et al*. showed that using CLD, mean setup errors are estimated to be 3.8 mm and 3.2 mm for systematic and random errors, respectively. In addition, the breast moves during respiration with a motion amount of 0.8-10 mm in the anterior-posterior (AP) direction.[18,19] Latifi *et al*. reported the respiratory-induced fiducial motion, based on the mean change in the fiducial's center of mass, was 0.8 ± 0.6 mm with a range of 0-2.2 mm.[20] Qi *et al*. estimated that respiratory-induced heart displacement for the left-sided breast irradiation results in variations in dose delivered to the heart up to 39%.[21] The discrepancy between the reported motion extents arises from several factors such as obesity, body mass index (BMI), the accuracy of the measurement technique, patient stress, the direction of the breast motion measurement, and patient age. It is shown that the target motion extent is more considerable in the AP direction compared to the right-left (RL) and craniocaudal (CC) directions.[22-25]

Motion monitoring techniques in breast cancer RT

Surface imaging

A promising solution for intrafractional motion monitoring in the chest wall irradiation and breast cancer RT is optical surface imaging.[26] Using three optical cameras and light projectors, the 3D map of a patient's topography is generated and allows visualization of the patient in any position or gantry angle (Figure 1).[27]

Surface imaging provides mobile target monitoring in the case of breast irradiation. Surface imaging is characterized by easy utilization and high temporal frequency without further radiation dose to the patient.[26] It can be matched with a variety of RT techniques (for example, breath-hold and respiratory gating) to reduce setup uncertainties

during delivery, which can lead to a reduction in target margins and nearby sparing. Several studies have shown that surface guidance for intrafractional monitoring was mainly utilized for breast breath-hold RT.[28,29] Additional benefits of surface imaging include (1) reducing interfractional setup error, (2) monitoring intrafractional motion, and (3) using less invasive patient fixation than other immobilization techniques, and more comfortability of patient as well.[30] However, surface guidance comes with some limitations. The visibility of the patient's skin surface for surface imaging is essential. Therefore, there is a compromise between surface imaging ability and the degree of immobilization. Also, any obstacle on the skin can lead to impossible reflectivity and restricting the function of surface imaging. An important limitation of surface imaging relevance to target localization is insufficient adaption between the external and internal surfaces. However, in breast cancer RT in which the external surface is the target surface, this problem becomes less important.[26] Nonetheless, surface-guided RT (SGRT) technology enables adaptive radiation therapy (ART) in which a motion history related to the patient is applied to perform narrower margins in the next following treatment fractions. Current applications of real-time surface imaging rely on breath-hold, respiratory gating, and tumor tracking deliveries.[31]

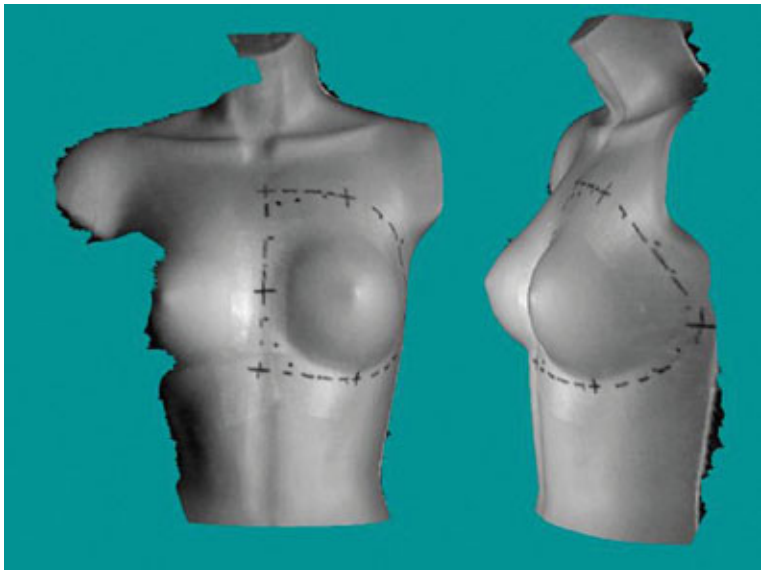

FIGURE 1. Anterior (left) and lateral (right) views of 3D surface images of the target left-sided breast using a 3D surface camera. With permission.[27]

Internal/external markers combined with real-time imaging

Accessibility of the breast (compared to deep organs such as liver or prostate) and typically shallow-seated targets, facilitate the application of internal markers.[32] Additionally, breast motion is well characterized by external markers.[33] Internal/external markers result in superior performance compared to the surgical clips in terms of both accuracy and detectability on kilovoltage (kV) images.[34] Organ displacement and real-time localization during beam delivery can be directly evaluated by employing external surrogate and/or internal radio-opaque fiducial markers. The fiducial marker tracking technique was first introduced for conventional RT and later for particle therapy.[32] Target motion tracking using internal markers is usually combined with more than two fluoroscopic imaging examinations. The fiducial markers are implanted near to or inside of the target. Markers (or surgical clips) are usually made from high-Z material such as gold, platinum, carbon-coated zirconium oxide to be visible in X-ray images.[35]

Using markers for motion monitoring in breast cancer, Kinoshita *et al*. showed the median range of respiratory motion is 1.0 ± 0.6 mm, 1.3 ± 0.5 mm, and 2.6 ± 1.4 mm for the RL, CC, and AP directions, respectively. The range of motion was the largest in the AP direction in all cases.[23,36-38] In a work by Korreman *et al*., it was reported that variability in motion patterns for target and surrogate using an internally placed gold marker and a reflective marker implanted on the chest wall can be considerable.[39,40] However, the difference between the surrogate marker position and the real tumor position in breast cancer is not a shortcoming as of other organs, mainly due to a good correlation between tumor displacement and that of the markers.

While fiducial markers find a wide range of applications in breast cancer due to the existing well signal correlation between tumor site and marker location, their usage is hampered by (1) the invasive nature of marker implantation, (2) possible displacement of the markers even more than few millimeters for tumor volumes far from the skin, (3) lack of volumetric information about anatomy deformations close to organ-at-risks (OARs), and (4) ionizing radiation imaging needed to localize them. Marker displacement from the implanted place, tumor deformation, and tumefaction of surrounding tissues are common reasons leading to such positional error[41,42] Artifacts in computed tomography (CT) images caused by high-Z fiducial markers are also problematic.[43] Electromagnetic

transducers/transponders (ET) are alternatives to high-Z internal markers providing continuous real-time 3D localization of the target without radiation imaging.[26] The Calypso system detects the fiducial marker location in real-time without X-ray imaging.[44] Commonly, three transponders with a variety of resonance frequencies (300-500 kHz) are placed in or close to the tumor. While the implementation techniques for ET are feasible and safe, they cannot be standalone. Several works indicate that interfractional variations of transponder location are significant and therefore hybrid real-time monitoring, for example, real-time tumor tracking is recommended.[45,46]

4D CT imaging

4D CT provides a high spatial and temporal resolution image of the thorax region during the planning phase to construct the breathing modeling used for managing respiration-induced motion. In other words, 4D CT enables 4D treatment planning. In 4D CT, the respiration cycle is first monitored by an external indicator such as real-time position management (RPM) system followed by dividing the cycle into several gates. Richter *et al*. showed motion amplitude of the chest in the 4D CT scanning is about 1.8±0.9 mm and target coverage was decreased by < 5%, caused by breathing motion.[47] 4D CT imaging/respiratory-correlated CT procedure is a promising solution for obtaining a time-resolved CT image at the cost of a substantial increase in radiation dose.[48-53]

Chan *et al*. showed a better estimation of the real amount of heart in the radiation field is possible using 4D CT imaging of the patient with breast cancer.[54] Qi *et al*. assessed respiration-induced heart motion by proposing two indices, the maximum heart depth (MHD) and the depth of the left ascending aorta (DLAD) extracted from the 4D CT dataset. They showed the dosimetric variation of the heart is highly correlated with these two metrics in gated RT for the left-sided breast cancer. Larger respiration-induced heart displacements (nearly 1 cm) are observed based on 4D CT scans. Also, a mean maximal dose to the left ventricle reduced from 49.14 (3D conformal RT (CRT)) to 33.97 Gy (intensity-modulated RT (IMRT)) when 4D CT imaging is used. The findings illustrated the potential use of 4D CT-based planning for cardiac sparing.[21] In a similar work, Yue *et al.* showed the changes (the difference between 4D and conventional plans) in D95, D90, V100, V95, and V90 of the target volume were -5.4%, -3.1%, -13.4%, -5.1%, and -3.2%, respectively.[12] In addition, V100 decreases from 81.8% in the conventional plan to 74.9% in 4D CT-based planning.[12] For evaluating cardiac sparing in tangential breast IMRT, Mahmoudzadeh *et al.* modeled the breathing-induced motion with deformable registration using 4D CT imaging in RT simulation in order to calculate accumulated heart dose for robust optimized and clinical plans.[55] Compared to the regular CT, the main drawback of 4D CT imaging for RT is the added radiation dose to the patient. The extra dose from the 4D CT imaging can be compensated by a substantial reduction of the RT dose to the OARs.[55]

4D and cine MR imaging

Recently, 4D magnetic resonance imaging (MRI) has been used to estimate respiratory motion variations and as a procedure to complement and support 4D CT enabling 4D RT planning and simulation.[56] Owing to superior soft-tissue contrast and radiation-free imaging features, MRI allows frequent multiple data acquisitions than CT. Due to limited time resolution associated with true 4D MRI, 2D cine-MRI is suggested.[57] Individualization of planning target volume (PTV) margin based on cine MRI data in the simulation seems to be a promising solution for the intrafractional motion problem.[58] Respiratory-correlated 4D MRI has attained more interest as an alternative to 4D CT for the measurement of respiratory motion.[59] Cai *et al.* presented the feasibility of 4D MRI using an image-based respiratory surrogate in the planning phase.[60] They investigated the accuracy of 4D MRI for motion measurement using 4D phantoms, for example, XCAT in terms of stability. Moreover, motion tracks can be estimated based on 4D MRI and 2D cine-MRI with an acceptable difference in motion amplitude up to -0.3 ± 0.5 mm.[60] 4D MRI provides an estimation of the respiratory motion for the two human subjects as much as 0.88 and 1.32 cm.[60] Also, Hu *et al.* showed a respiratory amplitude-based system to guide 4D MRI image acquisition is more robust to control irregular breathing compared to phase-based ones.[61]

Oar *et al.* performed a comparison between 4D CT and 4D MRI data quality based on the amplitude of motion in abdominal RT planning.[52] Motion uncertainty due to respiratory was estimated to be less than 0.2 mm in both the 4D CT and the ground truth; the median amplitude of motion was 11.2 mm and 10.1 mm for 4D CT and 4D MRI, respectively.[62] Paganelli *et al*. showed that the 4D MRI sequence enables describing organ motion and re-

duction of safety margins in RT planning.[63] Hurst *et al.* developed and optimized 4D MRI based on respiratory triggering using an external surrogate for abdominal tumors.[64] They concluded that any irregularity in patient breathing significantly affects 4D MRI performance. In addition, irregular and slow breathing rates deteriorate 4D MRI efficiency. A limitation of 4D MRI is, however, being sensitive to the change of breathing pattern between the preparation and acquisition periods. In addition, low temporal resolution is another limiting factor resulting in frequent scanner halts when breathing is irregular.[61] Long scan time is also uncomfortable for the patients. However, a reduction in acquisition time in a high field 4D MRI scanner is expected.[64]

Gantry-mounted X-ray imaging

Gantry-mounted X-ray imaging refers to those X-ray imaging modalities mounted on the treatment gantry allowing monoscopic and stereoscopic X-ray imaging. Portal imaging using electronic portal imaging devices (EPID) is a popular example of gantry-mounted imaging. Beam's eye view (BEV) portal imaging also enables real-time target motion tracking. Portal imaging is acquired with the help of the therapeutic megavoltage (MV) beam. Recently, gantry-mounted kV X-ray radiographic/fluoroscopic imaging is also available by either kV X-ray tubes or reduction of linac beam energy from MV to kV ranges.[47] The Vero, ExcaTrac, and CyberKnife systems offer stereoscopic imaging using two kV sources coupled with two flat-panel detectors.[26]

The acquisition of portal imaging is proved to be fast as well as easy to use in order to measure patient movement during breast cancer RT.[65] Richer *et al*. presented that tracking breast motion in EPID results in patient-specific maximum motion amplitude of from 0.8 to 2.2 mm, 1.5 mm on average.[25] In another work, respiratory motion during daily treatment on the CLD was investigated by EPID. The results of their work showed that intrafractional variation in each patient during treatment day was minimal. The daily maximum range for any patient was 0.25 cm.[17] For evaluating intrafractional and interfractional motion in breast cancer RT using EPID, Kron *et al*. concluded that the largest variation is in the CC direction with 1.3 ± 0.4 mm and 2.6 ± 1.3 mm for intrafractional and interfractional motions, respectively.[65] In a recent study based upon stereoscopic imaging enabled by the Cyberknife machine, Hoekstra *et al.* evaluated the effect of baseline and breathing motion on PTV margins for accelerated PBI (APBI) irradiation. They showed that the PTV margin depends on the treatment time.[66] However, poor image quality because of dominant Compton scattering in MV beams remains a major problem in portal imaging. Furthermore, according to the AAPM Task Group 75 report, a significant disadvantage of kV imaging-based motion monitoring is the extra dose to the patient, particularly at the skin surface.[67] Depending on the imaging technique, a typical dose of 1–3 mGy per image is delivered in any kV imaging.[26]

Ultrasound imaging

Rapid imaging along with no ionizing radiation makes ultrasound (US) imaging suitable for estimating intrafractional motion during the planning and simulation phases. The real-time US is also of interest in breast imaging mainly due to the lack of bony structures and also easy accessibility of the organ.[26,68] 4D US provides almost real-time 3D rendered image data and is considered as a basis of multidimensional imaging of the breast.[68] In addition, 3D/4D US of the breast provides diagnostic information of the coronal plane.[68]

US imaging typically provides good soft-tissue contrast and therefore allows contouring breast tumors. Furthermore, imaging artifact limits the application of real-time US imaging.[68-70] Because of its manual operation, the image quality is also user-dependent as well.[68] Despite well-established applications of US in diagnostics, target delineation, and pre-treatment localization, the use of real-time US imaging for intrafractional motion estimation and mitigation for breast cancer is limited and there is no commercially available system. The only commercial US system is Clarity Autoscan (Elekta) for monitoring intrafractional motion[26] that is approved specifically for prostate and/or prostate bed RT. However, Wong *et al*. applied the Clarity system to breast imaging to evaluate the error between the Clarity and pre-treatment CT images and observed that the errors are clinically insignificant.[71] However, in the era of surface imaging, the US methods cannot hold great advantages over ultrasound techniques for estimating breast intrafractional motion.[72]

Motion mitigation techniques in breast cancer RT

In the previous section, the main motion monitoring techniques of breast target were presented. The

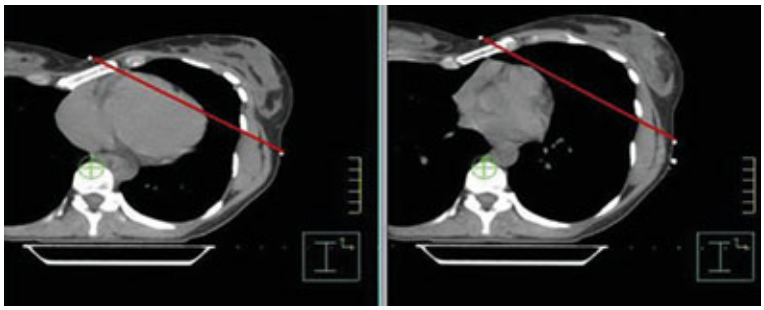

FIGURE 2. Heart position on axial CT slices of the same patient with breast cancer at free-breathing (left) and deep-inspiration breath-hold (DIBH) (right). The red line indicates the tangential treatment field border for whole-breast irradiation (WBI). With permission.[75]

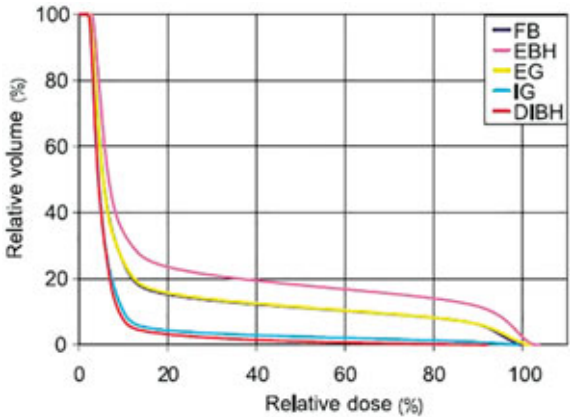

FIGURE 3. Comparison of whole heart dose-volume histogram in breathing adaptive radiotherapy for the same left-sided breast cancer patient for free-breathing (FB), end-expiration breath-hold (EBH), end-expiration gating (EG), end inspiration gating (IG), and DIBH plans. With permission.[96]

next step in the RT workflow is to assist the irradiation of mobile targets with motion monitoring data. Common irradiation approaches addressing the respiration-induced intrafractional motion in breast cancer treatment include breath-hold, respiratory gating, and real-time tumor tracking techniques. The influence of intrafractional target motion is of particular concern in APBI due to high doses per fraction, particularly for target volumes close to inhomogeneities (*i.e.*, skin or chest wall).[73,33] Therefore, motion mitigation techniques have to be perused in such treatment options.

Breath-hold

Breath-hold techniques refer to the management of target motion from the patient side. The deep-inspiration breath-hold (DIBH) method is a practical and easy-to-use solution for breast cancer RT.[6] During inhalation, the diaphragm moves the heart posteriorly and inferiorly away from the breast leading to a potential reduction of both heart and lung toxicities.[16] As illustrated in Figures 2 and 3, the major role of DIBH in motion-addressed breast cancer RT is increasing the distance between tumor volume and the heart leading to less dose to the heart and therefore a lower rate of toxicity.[74-76] DIBH is always linked to the beam gating to repeatedly on and off the irradiation beam based upon the patient respiratory cycle.

The DIBH for breast cancer RT is mostly employed in two manners: (1) moderate DIBH and (2) voluntary DIBH (vDIBH).[76,77] The former is also known as active breathing control (ABC) in the literature.[79] ABC uses special devices to control airflow during the respiratory cycle[77,78], while in vDIBH the patient is partially freely breathing. A decrease in the mean heart dose and the left artery dose to about 67% and 73%, respectively, is observed when using the ABC for breast cancer RT.[76] In addition, the ABC devices allow a reduction in setup uncertainties to less than 2 mm.[76] The vDIBH is sometimes used in conjunction with respiratory motion monitoring to capture breath function at certain points in the breathing period. As for the ABC, the vDIBH decreases the time for RT simulation and daily setup.[76,79] In contrast to ABC, vDIBH offers more patient comfort while it is also inexpensive.[75,79] Recently, the DIBH treatment using volumetric-modulated arc therapy (VMAT) is utilized for a patient with the left-sided breast cancer to irradiate both whole breast and regional node with superior target coverage and good cardiac sparing.[80,81]

Fassi *et al*. investigated target position reproducibility in the left-sided breast irradiation with DIBH using multiple optical control points. They compared the performance of optical surface imaging with that of the RPM-based methods and showed that the use of multiple surface fiducials leads to improved target and surface reproducibility.[82] Betgen *et al.* reported a systematic interfractional translation up to 5 mm and intrafractional errors of about 1.4 mm during voluntary DIBH using 3D surface imaging in patients with the left-sided breast cancer.[83] Borst *et al.* quantified the influence of breathing with DIBH in breast cancer RT. The percentage of the left ventricle (LV) irradiated volume was 28% and 71% for DIBH and free-breathing (FB), respectively.[84]

Respiratory gating

An efficient method of dealing with moving targets is to gate the radiation field. Respiratory gating refers to the management of target motion during treatment by rapid beam switching within the breathing cycle synchronized with an internal/external tracking system. Respiratory gating is usually implemented in two fashions: phase-based and amplitude-based gating. The former is accomplished by defining a set of phases (gates) over a complete breathing cycle. The irradiation beam is on in only one or few gates. In contrast, the latter is performed by setting a threshold value on the amplitude of the respiratory signal. Once the respiration signal falls below the predefined threshold, the irradiation beam is on. In a small gating window, the phase-based gating method can result in missing the tumor caused by interfractional position variations.

In contrast to the DIBH, the patient freely breathes while being irradiated with the therapeutic beam in respiratory-gated RT. Therefore, more patient comfort is obtained with respiratory gating.[85,86] Korreman *et al*. highlighted the dosimetric advantages of free-breathing gated breast cancer RT over vDIBH in terms of cardiopulmonary dose sparing.[73] Giraud *et al*. conducted a multicenter prospective study to compare respiratory-gated RT with conventional CRT for patients with breast cancer. They observed a significant reduction in lungs and cardiac toxicities when using the respiratory gating method.[87] Also, Qi *et al*. reported that the median heart volume receiving at least 50% of the maximum dose was decreased from 19.2% for free-breathing to 2.8% for end-inspiration gating. A substantial coronary artery volume sparing patients with the left-sided breast cancer was also observed. In addition, for both the right- and left-sided breast cancers, the median lung volume receiving 50% of the prescribed target dose reduced from 45.6% for free-breathing to 29.5% for inspiration gating.[21]

Respiratory gating results in two clinical benefits: (1) acceptable levels of target dose conformity and (2) OARs/normal tissues sparing. There are, however, several challenges associated with respiratory gating mandating further researches. First, time latency at the gating process has a result in underdosage and overdosage of proximal tissue. Thus, a successful gating process needs to minimize time latency during the gating window. Another challenge is a long treatment time by respiratory gating. The longer treatment time is inconvenient for the patients and can result in respiratory pattern variation, such as shift motion.[31] Another noticeable challenge for gated IMRT delivery is an increase in delivery time. The low efficiency of gated IMRT, as a product of the IMRT efficiency (20% to 30%) and the gating duty cycle (20% to 30%), results in a 10 to 25-fold increase in delivery time than conventional CRT treatments.[88]

To obtain benefits of the respiratory gating method, higher temporal resolution, higher soft-tissue contrast, and lower radiation exposure imaging techniques in the RT planning are mandated.[67] In some cases, however, motion occurs within the gate window, called residual motion.[88] Therefore, there is always a compromise between the amount of residual motion and the duty cycle to search for optimal gating parameters.[89] As heart dose automatically leads to an increase in cardiac mortality[90], a key question in respiratory gating is, therefore, the selection of optimal gating window parameters. Many studies have proved that the end of inspiration is optimal in terms of heart and lung tissue sparing in the left-sided breast cancer RT.[74,21] While the absolute lung volume irradiated is largest in respiratory-gated breast RT, the relative lung volume is smallest in the inspiration phases. Thus, the inspiration phases are optimal for beam gating in breast cancer RT by providing the longest distance between the breast and heart and also minimizing the lung density.[74] Although not implemented yet, respiratory gating based on the data from real-time cine MRI data would be a solution for online motion mitigation.

Real-time tumor tracking

Real-time tumor tracking is generally performed by either robotic radiosurgery, dynamic multileaf collimators (DMLCs), or couch movement.[91] Owing to the benefits of stereotactic body RT (SBRT), Cyberknife APBI can be considered as a real-time tumor tracking mitigating the intrafractional respiratory motion.[92] Methods like kV/MV radiographic imaging with and without markers, US imaging, portal imaging through EPID, kV/MV imaging are real-time tumor tracking methods. A combination of imaging methods with DMLCs (called dynamic IMRT) results in a solution for real-time tumor tracking.[93]

In breast cancer RT, real-time tumor tracking results in a substantial reduction in the volume of the heart receiving a high radiation dose.[93,94] Continues portal imaging during RT has shown promising results for estimating intrafractional chest wall mo-

tion of patients with breast cancer by providing time-resolved visualization of the internal organ from BEV.[95] As an estimate, Hijal *et al*. showed the irradiated volume of the heart of 30 Gy (V30) is 0.03% and 1.14%, and the mean heart dose is 1.35 Gy and 2.22 Gy, for real-time 3D CRT and static 3D CRT, respectively.[96] Leonardo *et al.* showed that real-time tumor tracking leads to significant heart sparing in a prone position in APBI and provides a daily precision treatment while reducing clinical target volume (CTV) to PTV margin.[93] In addition, in patients with abnormal anatomies as the significant volume of the heart may be irradiated, real-time tumor tracking would be useful to avoid extreme doses.[97]

MLC tracking has been successfully performed for IMRT and VMAT deliveries to address intrafractional target motion.[98-100] Dynamic IMRT enables dynamically reshaping the treatment field in the BEV based on the actually recorded target motion.[101] Furthermore, real-time tumor tracking with IMRT delivery resulted in better cardiopulmonary sparing and improved target coverage for breast cancer treatment.[102,103] While the dynamic IMRT provides a highly conformal dose distribution, it is usually challenged by the interplay effect that occurs in the time between leaf and the target motions. The interplay effect automatically leads to motion artifacts in dose distributions.[104,105] Synchronization of real-time tumor tracking based on two sets of fluoroscopy and IMRT delivery is also feasible but at the expense of non-negligible skin surface dose.[106] Real-time tumor tracking could also result in a percentage depth dose of 58% (at 5 cm) of the peak dose for long IMRT treatments.[26] In SGRT-based tumor tracking, beam-on and beam-off delays might play a role and vary between the SGRT system and beam delivery.[26] Smaller PTV margins are usually appropriate for patients with breast cancer who are actively monitored with surface imaging during RT.[107] Hamming *et al*. showed that SGRT data correlated well with CBCT data in patients with breast cancer.[108] In their study, the left-sided breast cancer was monitored continuously to maintain positional errors within 5 mm with SGRT.[108] The combination of real-rime surface-guided DIBH is also successfully implemented in patients with breast cancer, resulting in a reliable and stable DIBH treatment.[109]

However, some concerns associated with real-time tumor tracking are the resource-intensive nature of delivery and also imposing the amount of additional radiation dose.[110] According to the Report of AAPM Task Group 75 [67], a typical in-room kV cone-beam CT of the chest (commonly used in the case of breast cancer RT) leads to a maximum skin dose of 85.4 mGy. Real-time CBCT breast imaging results in a dose of 2 mGy and 12 mGy per scan for the right- and left-sided breast cancers, respectively.[110] Liu *et al*. showed that using 4D CBCT, PTV margin would be substantially reduced compared to kV CBCT treatments.[111] Real-time imaging during treatment increases RT irradiation time while the patient lies on the couch.[67] Real-time tumor tracking increases the complexity of the radiotherapy planning and delivery process, mandating rigid quality assurance at every level for precision and safe treatment.[101] Furthermore, the time delay between the real tumor position and the beam positioning system is a major challenge in real-time tumor tracking.[16] Besides, cycle-to-cycle fluctuations in the breathing cycle of the patient add complexity to the problem to some extent.[112] However, adaptive filter algorithms are proposed to predict tumor position in advance.[113]

The choice between prone and supine positions

Patient positioning (*i.e.*, supine or prone positions) plays a considerable role in motion mitigation techniques in patients with breast cancer.[114] Prone position refers to hanging the breast tissue under its weight through a hole at the bottom of the couch. Prone position improves separation between tumor and OARs as heart and lung for some patients. In addition, the prone position results in fewer respiration movements when compared to the supine position. Furthermore, some prone boards allow regional node irradiation, as well. However, the prone positioning is dependent on the position of the original tumor. In addition, patient setup variations can be significantly larger in prone positioning resulting in an increased interfractional variation.[115] In contrast, supine positioning is more common for staff and ease of setup. It can match nodal field to chest wall fields if this requires. Nonetheless, there is a lack of skin-sparing in women with large or pendulous breasts. Therefore, breast support by other devices is sometimes required to anteriorly position the breast away from the heart, lung, and abdomen. Referring to Figure 4, it is proven that the prone setup is more optimal for sparing lung volume compared to the supine position.[115,116]

Because of a significant decrease in irradiated lung volume and even irradiated heart volume in 87% of all patients with the left-sided breast cancer, the prone position outperforms the supine

setup by exhibiting improved dose homogeneity and fewer toxicities. Morrow *et al*. showed that the respiratory motion of the chest wall substantially decreases from 2.3 ± 0.9 mm to -0.1 ± 0.4 mm in supine and prone positions, respectively. They also showed that the prone positioning of patients for breast irradiation reduces the error introduced by intrafractional respiratory motion.[116] Veldeman *et al*. reported the 2-year better cosmetic outcome of prone positioning in comparison with supine positioning in large-breast patients.[117] To summarize, while supine positioning is the ease of setup, it is suboptimal in terms of lung and heart doses in some cases.[117]

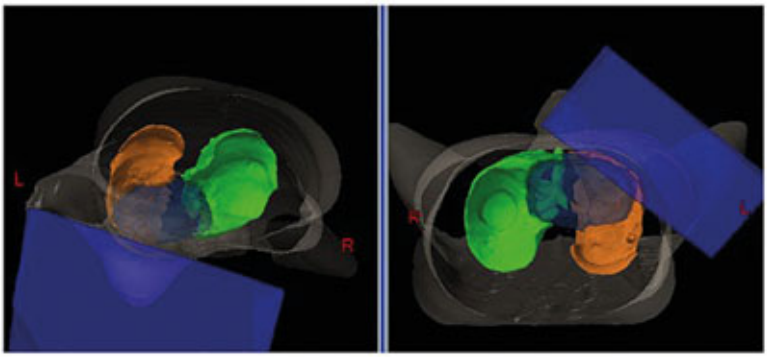

FIGURE 4. Comparison of cardiac sparing in prone (left) and supine (right) positions. The virtual blue box illustrates the in-field volume of the heart and lung by the Eclipse TPS. With permission.[115]

Target motion considerations in particle therapy

Particle therapy offers promising treatment outcomes and efforts have been continued to become a mature method for breast cancer treatment. Particle therapy commonly refers to the use of light/heavy charged particles such as protons, carbon-ions and helium-ions for cancer treatment. While active scanning and intensity-modulated proton therapy (IMPT) have become increasingly used in proton therapy, a great number of clinical researches are still published in passive scattering particle therapy (PSPT).[10,118] Compared to photon beam RT, particle beams are more sensitive to inline geometrical and density changes.[32,37,119] It is because of the particle interaction mechanism inside of the body.[32] In the monitoring of target motion benefiting from implanted surrogates, the high-Z internal markers can significantly alter dose distribution in particle therapy, and therefore thin (less than 0.5 mm in thickness) and low-Z materials, such as carbon-coated zirconium oxide clips, are preferred.[120] The degree of such an impact on charged particle dose distribution depends on the marker material, its position in the treatment field, and its thickness.[120] Similarly, Landry *et al*. showed that electromagnetic monitoring suffers from substantial distortions which bounded their utilization in a particle therapy.[121]

Breath-hold particle therapy is also an intrafractional motion mitigation technique in breast patients. However, in spot scanning beam delivery, the breath-hold technique cannot significantly reduce the heart dose mainly due to the so-called interplay effect.[5,6] Respiratory gating is also successfully translated into particle therapy to address the problem of the mobile target in breast cancer treatment.[37] Respiratory gating can be considered as a direct solution to the problem of dose degradation due to target motion as well as less dependency on the properties of the irradiation system. Similar to photon beams, respiratory gating for particle therapy faces two major challenges: (1) time latency that leads to over- and underdosage of the tumor and nearby tissues and (2) treatment prolongation that causes respiratory pattern variation.[32,122]

Intrafractional target motion management in active scanning particle therapy is hampered by the interplay effect. The interplay effect (interplay between intrafractional target motion and the beam spot position) is however approached by a new generation of particle accelerators, called Cyclinacs, enabling 4D spot scanning in particle therapy.[123] In a comparative study by Flejmer *et al*., respiratory gating proton therapy resulted in a reduction factor of 1.6 (from 0.5 Gy(relative biological effectiveness (RBE)) to 0.3 Gy(RBE)) in mean heart dose in the left-sided breast cancer compared to free-breathing proton therapy.[124] Siebenthal *et al*. studied the translation of 4D MRI from conventional RT to particle therapy to evaluate motion sensitivity and access the residual motion under different gating techniques.[125]

Patel *et al*. compared the dosimetric performance of photon and proton deliveries with and without DIBH.[126] They showed passively scattered proton beam delivery without DIBH results in slightly superior performance compared to the pencil-beam scanning during DBIH in terms of key metrics for avoidance structures. This is probably due to the interplay effect that exists in scanning deliveries. Another key conclusion of their study is that the cardiopulmonary toxicities in motion-managed particle therapy are not as high as those of photon therapy in breast cancer treatment. In another com-

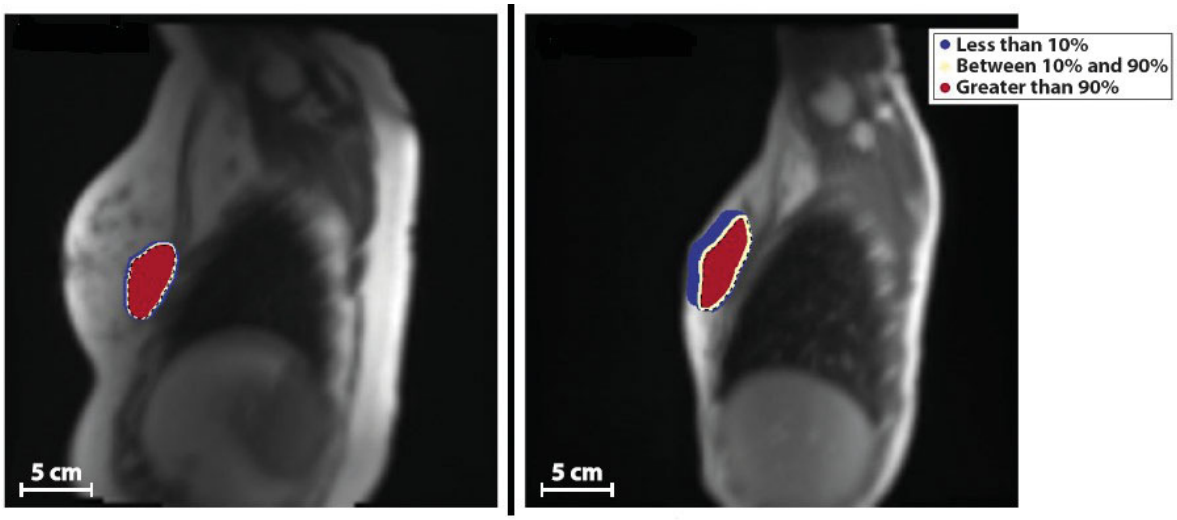

FIGURE 5. Heat map of fractional time that the surgical cavity occupies a given position during the MR-guided accelerated partial-breast irradiation (APBI) for two different patients with small (left) and large (right) displacements during the treatment delivery. With permission.[158]

parative study, Mondal *et al.* observed a significant dose reduction with proton DIBH compared to photon DIBH in terms of cardiac and pulmonary toxicities for WBI.[127]

The real-time tumor tracking approach for particle therapy is not well clinically available when compared to advance in-room imaging techniques in conventional photon beam therapy. Since particle therapy is much more sensitive to target motion when compared to conventional photon therapy, a combination of several motion mitigation techniques would be most beneficial.[128] Though most studies are centered on WBI, the influence of target size, location, breast size, and breathing cycle period is not well understood in APBI with particle beams. The effectiveness of respiratory gating for intrafractional target motion management for left-sided proton APBI needs to be also investigated. In addition, studies should be conducted to assess the impact of prone *versus* supine positions on the therapeutic outcome in terms of cardiopulmonary sparing, especially for thick or pendulous breasts.

Future directions

MRI guidance

MRI guidance is considered the future of image-guided RT (IGRT).[129] Real-time MR imaging is also safe in terms of radiation doses.[130] The state-of-the-art MR-linac integration in SBRT can provide tracking of the respiratory motion during the treatment fraction. A present limitation of an integrated MR-RT gantry is the high installation cost that limits its use in clinical practices. Acharya *et al.* determined intrafractional motion and evaluated delivered dose *versus* planned dose.[131] They demonstrated the mean difference of less than 1% between the planned and delivered dose using MR guidance for APBI delivery (Figure 5). They showed that a reduction in the PTV margin leads to a significant reduction in V50 and V100 for ipsilateral breast cancer MR-guided RT. When no additional PTV margin is applied, the mean cavity displacement in the AP and SI directions reaches 0.6 mm.[131]

Nachbar *et al.* in 2019, studied first-in-human APBI performed at a 1.5 T MR-linac for breast cancer using 7-beam IMRT delivery. Additionally, they have also investigated the influence of interactions of the secondary electrons with magnetic field on out-of-field dose.[132] Individualization of PTV margin based on cine MRI data from the simulation is also a possible motion mitigation method.[133] Although not yet implemented, real-time cine MRI-based beam gating seems also to be a promising solution.[133] Despite several advantages of MRI guidance, an open question, however, is a dose uncertainty observed in air-tissue interfaces where secondary electrons slightly contribute to total proton dose delivery.[133] Electron return and electron stream effects are two main concerns in treatment planning for a hybrid MR-linac delivery.[133] Although some existing challenges such as the selection of suitable coils and the above issues for breast cancer remain,

the first breast cancer was successfully treated with a hybrid MR-linac machine using an APBI technique.[133] Additionally, the magnetic field has a little negative impact on skin dose in APBI relative to WBI due to the use of smaller fields.[134]

Artificial intelligence in 4D RT

Artificial intelligence (AI) offers a set of key applications in RT workflow, including image segmentation (target and OAR delineation), image registration, radiomics, treatment response assessment/prediction, and tumor tracking. An interesting study showed that using single radiography, a whole 4D data is feasible to predict tumor movement during the treatment fraction using a deep convolutional neural network (DCNN).[135,136] Another role of AI in 4D RT is to create synthetic 4D CT from the 4D MRI dataset in MR-only treatment planning.[135] Chen *et al*. pointed out the usefulness of a deep U-net-based approach that synthesizes on-treatment CT-like images with accurate numbers from both planning CT and on-treatment CBCT. Based on their results, the proposed U-net can increase the accuracy of the CT number of CBCT, which makes possible further quantitative tools of CBCT, such as dose calculation and adaptive treatment planning.[137] The uses of AI in dynamic/4D breast imaging, image registration, and automatic cancer diagnosis are attracting a lot of attention.[138-140]

Rescanning for particle therapy

The rescanning (repainting) approach is proved to be effective in managing motion-induced dose uncertainty in actively scanned particle therapy to address the interplay effect.[141] However, some repainting methods mandate monitoring patient breathing to provide respiration parameters like period and rate.[142] For large target movements (> 5 mm), a combination of the repainting techniques with, for example, respiratory gating and breath-hold techniques lead to a superior outcome in terms of target dose uniformity. It should be mentioned that repainting techniques do not eliminate the use of safety margins entirely covering the target along with its movement extent. A potential pitfall of the repainting approach is a significant increase in total irradiation time.[142-144] Figure 6 shows the respiratory-correlated layered repainting method.[32] An iso-energy layer is irradiated in the gating window. The gating window is then divided into three portions, and therefore the number of rescanning is three.[32] While this method is proposed to be applied for lung cancer, its usefulness and applications in APBI are sparse and mandate extra researches.

Robust treatment planning

The term "robust treatment planning" refers to the incorporation of CTV-to-PTV margins into the optimization function during inverse treatment planning in IMRT techniques. The concept of robust treatment planning for breast cancer IMRT is utilized via RayStation TPS, as the sole TPS supporting robust optimization for IMRT.[54,145-147] Though, studies are shown that internal margin (IM) cannot be entirely eliminated in robust treatment planning.[53] Due to some uncertainties in particle therapy, for example, range uncertainty, the definition of simple PTV in particle therapy is suboptimal. Therefore, the role of robust optimization is to effectively address the tumor motion and uncertainties in RT, particularly in particle therapy.[145] Robust planning using VMAT delivery for a moving target in the breast generated clinically acceptable plans and was confirmed by real patient CBCT data.[147] Not directly applied for intrafractional motion management, the robust optimization for intensity-modulated proton therapy was used to address residual setup errors.[148]

Ultra high dose rate (FLASH) radiotherapy

FLASH-RT refers to ultra high dose RT with treatment time shorter than 0.1 s enabling excellent intrafractional motion management.[149] While maintaining local tumor control, FLASH-RT reduces normal tissue toxicity. Despite few clinical devices with the capability to deliver ultra-high dose rates, a lot of preclinical studies confirm the effectiveness of this paradigm-shifting technique.[150] In 2019, the first patient with T-cell lymphoma was successfully treated using FLASH-RT with the superior outcome on normal skin and the tumor.[151] Despite some technical challenges ahead, the combination of proton therapy (superior conformity) and FLASH-RT (shorter treatment time) can be a viable option for the treatment of breast cancer considering the intrafractional movements.

Conclusions

In this review, a comprehensive overview of the current and the state-of-the-art intrafractional target motion management in breast cancer RT was presented. Particularly, target motion considera-

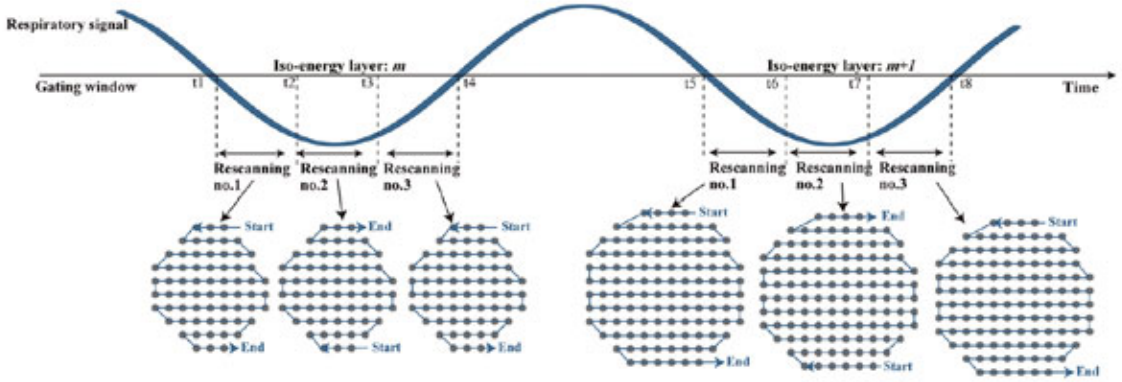

FIGURE 6. Schematics of iso-layered repainting in active scanning particle therapy. Three rescanning is applied within each respiration cycle. The middle rescanning (no. 2) has a reverse scheme as the scanning starts from the bottom and ends at the top. With permission.[33]

tion for particle therapy for breast cancer is highlighted. Several techniques available for monitoring intrafractional target movements such as surface imaging, kV/MV imaging with and without markers, 4D CT, 4D MRI, and the real-time US are discussed. Future perspectives for mitigating intrafractional motion, for example, MR guidance, and FLASH-RT are also highlighted. Almost all of the available remedies are directly applicable to breast cancer, mainly since it is an easily accessible organ. However, the SGRT technique seems to be the dominant motion-managed RT strategy for breast cancer. The problem of intrafractional target motion is more challenging in particle therapy, and therefore further research and development efforts still need to be performed to take the full advantages of the presented methods and to address the open questions in technical and clinical issues related to irradiation of mobile targets seated in the breast.

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