New Advances in Breast Cancer Radiotherapy

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Abstract

Radiation therapy has undergone immense growth in knowledge, technology, and precision. Treatments for breast cancer have evolved from sole reliance on bony anatomy and clinical set-up to detailed dose measurements to organ substructures. Imaging techniques have evolved from 2-dimensional (2D) to 3-dimensional (3D) with the standardized use of computed tomography simulation and target delineation. Advances in technology with intensity-modulated radiotherapy and volumetric modulated arc therapy have increased high-dose conformity and low-dose normal-tissue exposure. Proton therapy is emerging as a modality that can minimize the compromises between target coverage and avoidance of organs at risk. Although not yet in clinical use, a significant step in precision radiotherapy is on the horizon: the use of genomics, which may allow tailored radiation doses based on the genetic make-up of the tumor and patient-specific factors conferring radiosensitivity or radioresistance.
Introduction

The benefit of radiation therapy in the treatment of breast cancer has been well-established. While a multitude of radiation techniques can be used to treat breast cancer, all are directed by the simultaneous goals of covering the target and avoiding organs at risk (OARs). While various studies have shown improvements in local-regional control, disease-free survival, and overall survival with the use of radiation therapy for breast cancer, toxicity to the nearby normal tissue can detract from the therapeutic ratio. Even with significant improvements in systemic therapy in recent years, modern studies continue to show a benefit to radiotherapy. Reduction in target volume with partial breast irradiation and cardiac-sparing techniques, such as deep-inspiration breath hold and prone positioning, have contributed to show improvement in the therapeutic ratio.

In one study, randomization to irradiation of the whole breast and regional lymphatics compared to whole-breast irradiation alone resulted in improved 10-year disease-free survival (DFS) (82 percent vs. 77 percent, respectively; \( p=0.01 \)).\(^1\) A similar study comprised of 44 percent high-risk node-negative patients and 24 percent mastectomy patients also showed a 3 percent improvement in 10-year DFS with the addition of supraclavicular (SCV) and internal mammary node (IMN) irradiation compared to irradiation to the breast or chest wall alone (72.1 percent vs. 69.1 percent; \( p=0.04 \)).\(^2\)

Target and normal tissue delineation (contouring)
Historically, radiation was delivered based on bony anatomy as seen on x-rays or fluoroscopy. Using computed tomography (CT) to direct the location of the radiation therapy portals was initiated in the 1990s. By the early 2000s, CT-based treatment planning was routinely used, with CT scanners becoming available within most radiation oncology departments in the United States. The transition from 2D to 3D imaging allowed for the ability to define 3D targets. Targets (gross disease or areas at risk for microscopic disease) and adjacent tissues, such as OARs, are delineated on the CT imaging using various treatment planning systems. While contouring has been implemented for different diseases at different rates, contouring has had a slow rate of adoption in breast cancer. In fact, the first Radiation Therapy Oncology Group (RTOG) protocol that required contouring in treatment of the whole breast opened in 2011.3

Delineation on CT allows the dose to a structure (such as a target or OAR) to be determined, including the minimum dose, the maximum dose, and the amount of dose to a certain volume.4 Goals for target coverage and limits for OARs are used to guide treatment planning. In an iterative process, if target coverage is suboptimal or the OAR dose is exceeded, the dosimetrist changes the plan design to find a better solution. Without contours, the dose distribution can be visually assessed, but dose-volume relationships cannot be determined.5,6

With the transition to contour-based planning, it was recognized among experts that variation existed in the definitions of the targets and OARs.7 In an attempt to standardize these structure definitions more than five years ago, the RTOG published an online contouring atlas based primarily on muscle and bony anatomy.8 Since that time, several investigators have assessed the comprehensiveness of this contouring atlas. Brown et al reported that in 39 percent of patients, disease in the supraclavicular region occurred outside of the volume suggested by the RTOG atlas.9 Jethwa et al reported that 22 percent of disease fell outside of the recommended internal
mammary node volume. A 3- to 4-cm expansion beyond the RTOG axillary nodal volume in the anterior and cranial directions for the level I (low) axilla was recommended by Gentile et al. A revised atlas by NRG Oncology (the cooperative group that replaced RTOG) is in development. Other contouring atlases were developed after the seminal RTOG atlas. The Danish atlas was based on expert consensus and the use of vessel location as well as muscle and bone anatomy. The PROCAB/ESTRO (PROject on CAncer of the Breast/European Society of Radiation Oncology) guidelines are vessel-based and centered around a 5-mm margin on the veins in the regional lymphatic regions.

While these atlases provide guidelines, they are not meant to prohibit adjustments to each individual case. Particularly for those who present with node positive disease, fusion of the imaging at diagnosis (including positron emission tomography (PET) and magnetic resonance imaging (MRI) to the CT simulation images) can ensure that the area that previously harbored gross disease is fully covered with sufficient dose to eradicate any microscopic residual disease (Figure 1A). Early referral to radiation oncology allows assessment of the disease at presentation, which may alter the radiation fields. Once the disease has regressed with systemic therapy, or been excised with surgery, the opportunity for the radiation oncologist to tailor the radiation fields based on initial disease presentation has passed (Figure 1B). Surgical clips to demarcate the lumpectomy bed allow the boost volume to be accurately defined. Surgical clip demarcation is important in all breast-conserving cases, but is absolutely critical in oncoplastic reconstructions and for external-beam partial-breast irradiation.

**Advanced delivery techniques**
With 2D or 3D treatment planning, contouring contributes to a high-quality plan, yet it is not a required step in the treatment planning process. A plan can be created in the absence of contours and reviewed based solely on isodose distributions. However, for more advanced treatment planning, such as step-and-shoot intensity-modulated radiation therapy (IMRT), arc therapy, or proton therapy, a treatment plan cannot be generated without contours as dose is prescribed to a delineated volume rather than a point. With these planning techniques, the high dose achieves tighter conformality around the target volume. Therefore, the target delineation is a critical step in the treatment planning process upon which all of the subsequent steps hinge. Prioritization of target coverage and OAR goals may be necessary and may depend on the clinical situation.

Treatment plan evaluation includes a review of the radiation dose distribution achieved by a particular plan, which designates field size and shaping, number and angle of fields, weighting of fields (how much dose is delivered through a given field), and technique. The robustness, or reliability, of the treatment plan must be considered. Factors such as treatment delivery time, respiratory motion, potential change in anatomy, such as variation in seroma size, are assessed. Other variables, like thorax shape, proximity of the heart to the chest wall, breast size and shape, presence of expanders, and implants, can impact radiotherapy dosimetry and contribute to decisions about the optimal radiation modality. In women with left-sided breast cancers, the proximity of the left anterior descending artery and left ventricle to the chest wall can present a challenge, particularly if the IMNs are treated.

3D conformal photon radiation therapy (3DCRT) remains a common form of treatment for breast cancer. This technique is robust in that modest changes in breast size or shape or changes in seroma are unlikely to affect the dosimetry (Figure 2). While the high dose may not be as conformal as IMRT or arc techniques, the low dose tends to be more confined compared to these
approaches. A common beam arrangement consists of parallel-opposed photon tangent fields to
treat the breast or chest wall, IMNs, and low axilla, matched to an anterior photon field that treats
the high axilla and SCV nodes. Smaller fields may be inserted within a larger field or dose-
absorbing wedges may be placed in the beam path, particularly in tangential fields, to modulate
or improve dose homogeneity. Electrons may be used to treat superficial targets, such as a thin
chest wall or some lumpectomy cavities. With 3DCRT, a dosimetrist selects the beam angles and
evaluates the dose distribution to maximize target coverage and OAR constraint goals in an
iterative fashion.

IMRT uses multiple beams (typically 5 to 7) to achieve conformality of the high dose
distribution to the target volume. Unlike 3DCRT, with IMRT, the target coverage and OAR
constraint goals are entered into the treatment planning system, and the system selects beam
angles and shapes. Volumetric modulated arc radiotherapy (VMAT) is a type of IMRT that also
achieves high dose conformality with faster delivery time.\textsuperscript{18} While IMRT uses multiple
independent beam angles, VMAT delivers radiation continuously in an arc as the gantry rotates
around the patient. Multiple parameters can be adjusted during this dynamic delivery, such as
field shape and orientation, dose rate, and rate of gantry rotation.\textsuperscript{19} These techniques yield high-
dose conformality, but often expose larger volumes of normal tissue to low-dose radiation
compared to the 3DCRT technique (Figure 3); for example, there may be an increase in the
volume of heart receiving 5 Gy,\textsuperscript{18} a parameter associated with an increasing risk of cardiac
disease. One dosimetric study predicted an increased risk of contralateral breast cancer with the
use of IMRT compared to conventional 3D technique, but not with VMAT.\textsuperscript{20} In a dosimetric
study comparing VMAT and conventional 3DCRT, VMAT achieved high dose conformity and
lower mean heart doses, but the dose to the contralateral breast and/or lung increased.\textsuperscript{21} Five
randomized trials comparing IMRT to 2D or 3DCRT\textsuperscript{22,23,24,25,26} have shown a reduction in acute radiation dermatitis with the use of IMRT.\textsuperscript{27}

Protons differ from photons in that they are particles rather than energy, they have mass, and they travel only a finite distance. With proton therapy, the depth of penetration into tissue can be controlled, thus there is no exit radiation dose beyond the tumor target. In addition, less dose is deposited along the entrance path compared to photons. Protons deposit most of the dose at the end of their path in a sharp peak of energy deposition called the Bragg peak (Figure 4). Therefore, with protons, most of the dose is deposited in the target compared to outside of the target with photons (regardless of photon technique, be it 3DCRT, IMRT, or VMAT).

In the use of proton therapy for breast cancer, anterior \textit{en face} beams are aimed directly at the target in the direction of respiratory motion, rather than tangentially, minimizing the risk of loss of target coverage during respiration and improving the robustness of the proton plan. The \textit{en face} beam orientation also allows for a choice of treatment with arms akimbo rather than overhead, which may increase patient comfort during treatment delivery. The abrupt dose fall-off permits coverage of all target areas, including the internal mammary nodes, while simultaneously achieving little or no dose to the heart (Figure 3). A median mean heart dose of $< 1$ Gy, even with IMN treatment, has been consistently achieved in multiple studies of proton therapy for breast cancer.\textsuperscript{28,29,30,31,32} The dose can be modulated to maximize radiation avoidance to cardiac substructures, such as the coronary arteries. Proton therapy for unilateral breast cancer typically eliminates the dose to the contralateral lung. In the setting of regional lymphatic irradiation, the volume of ipsilateral lung receiving 5 Gy and 20 Gy is often decreased by 50 percent compared to 3D conformal photon therapy treatment.\textsuperscript{30,32} Compared to IMRT, proton therapy also delivers significantly less low-dose radiation (V5, V10) to the lung with reduced or similar moderate-to-
high-dose radiation (V20, V40).²⁸,²⁹ Of all currently available techniques, proton therapy yields the lowest overall integral dose (dose to non-targeted tissue).³² With the decreased integral dose and lung dose as well as elimination of contralateral breast/chest wall dose, proton therapy may decrease the rate of second malignancy.³³

Proton therapy can be delivered with passive-scattering (double-scattering or uniform scanning) or with scanning (intensity-modulated proton therapy [IMPT]) techniques. The skin dose can be higher with proton therapy compared to photon techniques, increasing the risk of radiation dermatitis. With IMPT, modulation can be used to decrease the dose to skin, but passive-scattering does not allow for this.³⁴

While all aspects of breast cancer radiotherapy operate within guidelines, each step in the process is individualized depending on patient needs, including positioning (supine or prone; with protons, arms up or akimbo), target delineation (adjusted based on review of initial imaging; decision on which nodal volumes are at high enough risk to warrant treatment; partial or whole breast treatment), and modality (photon vs. electron vs. proton; 3DCRT vs. IMRT vs. VMAT with photons; double scattering vs. scanning proton therapy). In addition, the prescription dose is largely empirical, based on historical studies, with minimal variation between patients. These treatment planning decisions are made after evaluating patient and disease characteristics, but rarely on genomics.

**Genomics**

Data continues to emerge on the association between recurrence score and local-regional failure. If validated in ongoing prospective studies, the recurrence score may become an important tool
in selecting patients with favorable biology for whom radiation therapy may afford minimal
benefit versus those with unfavorable biology for whom radiation therapy may have a significant
impact. An analysis of combined retrospective data from NSABP B14 and B20 evaluated women
with node-negative, ER-positive breast cancer. Even for these luminal breast cancers, recurrence
score correlated with local-regional recurrence, and this association persisted regardless of the
type of systemic therapy administered. From this data set, subgroups that would benefit from
radiation can be identified. In an analysis of women with node-positive breast cancer enrolled
on the NSABP B28 trial, recurrence score again correlated with local-regional failure,
contributing prognostic information beyond the traditional clinical factors such as the number of
involved lymph nodes.

Routine testing for individual tumor sensitivity to radiotherapy appears to be on the horizon.
Investigators who underwent an in-vitro study of 16 breast cancer cell lines found that, after
exposure to 2 Gy, the surviving fraction ranged from 17 percent to 77 percent. A 51-gene
radiosensitivity signature was then developed, which predicted local-regional failure better than
traditional clinical factors, with a sensitivity of 84 percent and a negative predictive value of 89
percent. In 2015, Torres-Roca et al identified radioresistant and radiosensitive populations in a
cohort of over 300 patients treated with adjuvant radiotherapy by combining the radiosensitivity
index and molecular subtype. The triple-negative, radioresistant group had a higher risk of local-
regional failure than the triple-negative, radiosensitive group, whose local-regional failure rates
were comparable to those with luminal breast cancers. A luminal, radioresistant cohort was also
identified. One year later, Scott et al combined a genomic radiosensitivity index and the
radiobiologic linear quadratic model to create the genomic-adjusted radiation dose model. Such a
model may allow prospective trials to test and validate these promising genomic assays along a
sliding scale of radiation dose, from omission of radiation to dose de-escalation to dose escalation. Late radiation toxicity may also be influenced by genomics. Knowledge of patient susceptibility to radiation injury of healthy tissue could triage patients towards a certain radiation modality or delivery technique. Those most sensitive to radiation damage may benefit most from advanced, maximal organ-sparing techniques, such as proton therapy. An expert panel convened at the National Institutes of Health in 2016 to review the current status of genomically guided radiotherapy and outline the journey ahead to move from the lab to the bedside with individualized, precision radiotherapy.

Conclusion

The optimal radiation technique to treat breast cancer may vary with the treatment volume, patient anatomy, and laterality of the breast cancer. However, the initial step of accurate target and OAR delineation is essential to high-quality radiotherapy regardless of delivery technique. Current challenges include reducing radiation exposure to normal, non-targeted tissues (especially the heart and lung) while improving the coverage of critical breast cancer targets, such as regional nodes. Compared to conventional 3DCRT, the use of IMRT and VMAT improve conformity of the high dose to the target regions but at the expense of exposing a greater volume of uninvolved adjacent tissue (contralateral breast and lung) to low radiation doses. Proton therapy improves target coverage, achieves conformity of the high-dose volume to the target, and significantly reduces both OAR and integral doses. Advanced radiation techniques may further enhance the therapeutic ratio through increased target coverage and/or reduction of critical organ exposure and allow for dose escalation, intensification, or hypofractionation to further improve outcomes. Genomic analysis for tumor and healthy tissue radiosensitivity appears to be a key step in the forward progress of precision radiotherapy,
allowing for tailoring of radiation dose and modality. Significant improvements in patient outcomes are anticipated with these novel techniques, but a minimum of 10 years of follow-up will be necessary to confirm expectations.

References


Figure Legend

Figure 1: (A) Tumor involving an inframammary crease warrants a generous inferior border of the radiation field to ensure adequate coverage of tissue at risk for harboring microscopic disease. (B) Supraclavicular nodes extending posteriorly, beyond typical contouring guideline recommendations, highlights the need for adaptation of the guidelines to the individual patient.

Figure 2: (A) An image from a computed tomography verification scan at fraction 10 of radiotherapy shows a new seroma posterior to the expander at the inferior aspect (top image) that was not present on the CT simulation images (bottom image). (B) The 3-dimensional conformal dose distribution was not affected by the seroma development.

Figure 3: Comparison treatment plans for a patient with breast cancer, including (A) 3-dimensional conformal radiotherapy, (B) intensity-modulated radiotherapy, (C) volumetric modulated arc therapy, (D) and pencil-beam scanning with protons.

10% of the prescription dose is shown in orange, 50% in green, 90% in light blue, 95% in pink, and 110% in dark blue.

In (A), there is a small amount of high dose to the heart but less low dose compared to (B) and (C). In (B) and (C), there is less high dose to the ipsilateral lung but an increased volume of low dose. In (D), both low and high doses are eliminated from the heart and lung while maintaining 95% coverage of the targets (the breast and internal mammary nodes).

Figure 4: (A) The path of a single proton as it enters the body and deposits the vast majority of its energy at a single point. This phenomenon is referred to as the Bragg peak. Oncologists can manipulate the deposition depth by controlling the speed of the proton in addition to controlling the target area, thereby reducing radiation to normal tissue. (B) A comparison of the amount of
radiation delivered with conventional photon radiation therapy versus proton therapy.

Conventional therapy is distinguished by a relatively high entrance dose and exit dose. By contrast, proton therapy has a much lower entrance dose and no exit dose. The goal in radiation therapy is to minimize damage to healthy tissue by minimizing the tissue exposed in the entrance and exit doses. Borrowed with permission from UF Health Proton Therapy Institute.
Figure 4

A

The Bragg Peak of Protons

Amount of Radiation

Depth in the Body (cm)

B

Proton Deposition Curve

X-ray Deposition Curve

Amount of Radiation

Depth in the Body

ENTRANCE DOSE

EXIT DOSE

TUMOR
New Advances in Breast Radiotherapy CME Test

Return by May 1, 2021 by Email to kristy@dcmsonline.org

1. How does the RTOG contouring atlas define target nodal areas in the treatment of breast cancer?
   a. 5mm margin around vessels
   b. bone and muscle
   c. based only on pre-treatment imaging
   d. definitions vary based on patient age and body mass index

2. The purpose of clips placed in the tumor bed at the time of surgery is to:
   a. decrease the risk of infection
   b. minimize post-operative risk of bleeding
   c. improve accuracy of post-treatment mammogram surveillance
   d. ensure full coverage of the tumor bed with the prescribed dose of radiation

3. Evaluation by radiation oncology early in the work-up and assessment of a patient is important because:
   a. radiation should be the initial step in breast cancer treatment.
   b. CT simulation is required prior to the start of other therapies.
   c. radiation dose and fields may be tailored based on clinical findings at initial diagnosis.
   d. the radiation modality should be determined at that time.

4. Which of the following factors does not affect plan robustness?
   a. prescription dose
   b. respiratory motion
   c. treatment delivery time
   d. change in seroma

5. Advantages of 3D conformal radiation therapy over IMRT or VMAT include all of the following except:
   a. less low dose exposure to normal tissues
   b. less sensitive to daily differences in patient set-up
   c. increased conformity of high dose
   d. increased robustness in the setting of breast edema

6. Which of the following modalities uses a continuous arc to deliver radiation dose?
   a. 3D CRT
   b. IMRT
   c. VMAT
   d. Proton therapy
7. Which modality eliminates the exit dose beyond the target volume?
   a. 3D CRT
   b. IMRT
   c. VMAT
   d. Proton therapy

8. The sharp fall-off of dose at the end of the proton path is called the:
   a. given dose
   b. Bragg peak
   c. beam angle
   d. Compton effect

9. One advantage of proton therapy compared to IMRT or VMAT is:
   a. decreased dose to adjacent organs such as heart, lung and contralateral breast
   b. increased conformality of high dose
   c. decreased skin dose
   d. target contouring is not necessary

10. What is the sensitivity of the 51-gene radiosensitivity signature?
    a. 17%
    b. 51%
    c. 77%
    d. 84%