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Potential Morbidity Reduction With Proton Radiation Therapy for Breast Cancer

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Proton radiotherapy confers significant dosimetric advantages in the treatment of malignancies that arise adjacent to critical radiosensitive structures. To date, these advantages have been most prominent in the treatment of pediatric and central nervous system malignancies, although emerging data support the use of protons among other anatomical sites in which radiotherapy plays an important role.

With advances in the overall treatment paradigm for breast cancer, most patients with localized disease now exhibit long-term disease control and, consequently, may manifest the late toxicities of aggressive treatment. As a result, there is increasing emphasis on the mitigation of iatrogenic morbidity, with particular attention to heart and lung exposure in those receiving adjuvant radiotherapy. Indeed, recent landmark analyses have demonstrated an increase in significant cardiac events that is linked directly to low-dose radiation to the heart. Coupled with practice-changing trials that have expanded the indications for comprehensive regional nodal irradiation, there exists significant interest in employing novel technologies to mitigate cardiac dose while improving target volume coverage.

Proton radiotherapy enjoys distinct physical advantages over photon-based approaches and, in appropriately selected patients, markedly improves both target coverage and normal tissue sparing. Here, we review the dosimetric evidence that underlies the putative benefits of proton radiotherapy, and further synthesize early clinical evidence that supports the efficacy and feasibility of proton radiation in breast cancer. Landmark, prospective randomized trials are underway and will ultimately define the role for protons in the treatment of this disease.

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Introduction

Adjuvant radiotherapy (RT) confers significant local control and overall survival benefits for breast cancer patients, in both the breast conservation and postmastectomy settings.[1-3] However, despite clinical and technological improvements in RT delivery, there remains a measurable risk of adverse effects that stems largely from the obligate exposure of adjacent normal structures, either directly to the radiation beam or indirectly to scatter. For example, conventional photon-based breast radiation necessarily exposes the lungs and heart to some degree, resulting in pneumonitis within months of treatment in a small percentage of patients,[4,5] or long-term cardiac injury (eg, cardiomyopathy, valvular dysfunction, coronary artery disease, and cardiac death) within years.[6-10] To counter this physical shortcoming of X-ray radiation, proton-based RT was developed, employing this charged-particle beam that has physical properties permitting coverage of a deep target with essentially complete avoidance of exit dose to underlying structures beyond the target volume(s). The clinical, dosimetric, and physical properties of proton RT in the treatment of breast cancer will be discussed in detail later.

Importantly, however, proton RT is also more costly than comparable photon-based technologies. As a result, proton treatment centers have historically been limited to major institutions within the largest population centers. More recently, however, data have begun to emerge demonstrating the significant clinical advantages of protons in select settings. Single room proton facilities have also emerged, markedly decreasing the initial capital cost to enter the market and allowing smaller hospital systems that serve smaller patient populations to consider proton therapy. This has prompted a rise in global interest[11] and a rapid expansion in the number of

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centers that has broadened the availability of this technology.[12] This surge of interest, coupled with market forces and contemporary resource constraints, make it imperative that clinical leaders carefully evaluate the implications, costs and benefits of proton therapy, particularly in an era of advanced photon and electron-based alternatives.

Emerging data suggest the potential for protons to mitigate the toxicity of RT in select settings. In contrast to megavoltage photon-based radiation, a proton beam is comprised of particles with mass and charge that exhibit distinct tissue interactions. A proton beam, upon encountering tissue, deposits a moderate and constant dose until nearing the end of its range where most dose is deposited within a short distance. The dose deposition profile of a proton beam is, therefore, characterized by a long plateau followed by a sharp peak (the "Bragg peak") and an abrupt drop-off. As a result of the abrupt halt in the terminal portion of the proton range, nearly no dose is delivered beyond a given depth. Therefore, whereas photon radiation necessarily confers an "exit dose", protons yield no such additional exposure beyond the target. This physical property is of particular significance for breast cancer patients as it permits mitigation of both high and low dose exposure to pulmonary and cardiac structures among other adjacent tissues (Figure 1). These physical properties, and the absence of exit dose in particular, confer the major advantages of proton therapy in limiting exposure to adjacent normal tissues and, in turn, potentially reducing the overall likelihood of toxicity. Several trials are currently underway to assess the clinical significance of these physical and dosimetric advantages, including a large-scale randomized national study which seeks to compare proton vs photon outcomes (RADCOMP—Clinicaltrials.gov: NCT02603341).

In the setting of historically low recurrence rates and the rising prevalence of early-stage disease largely owing to widespread screening, the reduction of treatment-associated morbidity is of particular importance. Rising mastectomy rates and enhancements in reconstructive approaches also now challenge the most advanced photon-based approaches to optimize conformality while minimizing toxicity. Moreover, with the recent publication of MA.20[13] and EORTC 22922,[14] two trials that demonstrated the benefits of regional nodal irradiation in patients with high risk, early stage breast cancer, comprehensive regional RT including the internal mammary nodes, is increasingly being employed and further pushing the technical boundaries of traditional radiotherapeutic approaches. The physical properties of protons allow for the targeting of the whole breast, chest wall, regional nodal basins, or implant reconstruction while simultaneously minimizing dose to adjacent normal tissues. With the anticipated favorable outcomes for most breast patients, proton radiotherapy heralds an opportunity to deliver comprehensive treatment while optimizing iatrogenic risk.

Indeed, among the most concerning late effects for this population is cardiac morbidity.[15] Insult to the heart from radiation has been reported in many forms, including direct injury to the myocardium or coronary vessels that lie adjacent to the target chest wall.[16] Premature coronary disease has been seen in the mid and distal left anterior descending artery among those with left-sided lesions, and right coronary disease for those with right-sided tumors.[17,18] Cardiac dose and therefore, risk, is elevated among those who must receive treatment to the internal mammary nodes, which often lie in direct apposition to the pericardium. In a landmark study that elucidated cardiac risk, Darby et al[19] demonstrated that mean heart dose is directly associated with cardiac outcomes, with the relative risk of a major cardiac event increasing linearly by 7.4% per Gray increase in mean heart dose. Of note, there appeared to be no lower bound for this association, suggesting that even at low mean heart doses, subsequent cardiac risk was elevated above baseline. In addition, although cardiac morbidity often manifests >10 years after treatment, the increased cardiac risk appears significant even in the early years following treatment.

It is important to note that contemporary photon-based approaches have seen considerable advances in treatment conformality. Among the most revolutionary of these has been intensity modulated radiation therapy (IMRT), which leverages computational modeling to develop treatment plans of increasing complexity, conformality, and homogeneity. These improvements are enabled by algorithms that iteratively modulate treatment beams to optimize the plan around defined targets and organs-at-risk. However, by employing multiple beams and subfields to convert high dose regions into lower-dose swaths, IMRT necessarily increases the volume of tissue receiving low-dose exposure. This increase in volume of exposed tissue is of particular significance among young patients who will face the risk of secondary malignancies several decades following treatment.[20-23]

In treating breast cancer, IMRT typically increases the low-dose exposure of the heart and lungs with limited short-term consequences,[24] but with unclear long-term implications which remain under study. A recent study showed that even low-dose exposure to the left ventricle (V_5) may lead to serious cardiac morbidity, raising concern about the increased volume of the low-dose IMRT region.[25] This low-dose spread can ultimately be limited by simplifying IMRT plans to include fewer fields, or by using 3D-conformal therapy (3D-CRT), although at the expense of target conformality and coverage. Deep inspiratory breath hold (DIBH) has also emerged as an effective technique to limit unwanted cardiac exposure.

Because of the difference in physical interactions between proton and photon beams, proton treatments are prescribed in Relative Biologic Effectiveness; Gy[RBE] (Gray-RBE), in contrast to the conventional Gray. This annotation denotes the higher biologic effectiveness per unit of proton radiation and is used throughout this discussion. To calculate this biological dose, the physical dose is multiplied by a factor of 1.1 in contemporary practice, largely based on prior radiobiologic studies in animal models. Indeed, RBE may vary with α/β, with fractionation, or at the distal edge of the Bragg Peak. In the future, LET-based planning may be possible, but the 1.1 factor has been in clinical use for decades with reproducible outcomes. As defined, a given photon dose in Gy is expected to yield similar cell-kill as the same numeric proton dose in Gy (RBE).