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TREATING BREAST CANCER WITH PROTON THERAPY

CURRENT PRACTICE, OPPORTUNITIES AND CHALLENGES

Proton Therapy in Practice: Clinical Indications - Breast Cancer

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PROTECT + ENHANCE + SAVE LIVES

FOREWORD

Since IBA first started to develop proton therapy solutions, we have focused on collaboration and sharing information. This culture of cooperation allows us to work collectively with clinical partners to make proton therapy available to anyone who needs it.

Our purpose is simply to offer more cancer patients effective treatments, decreased late effects, and a better quality of life.

The amount of clinical data on proton therapy is increasing rapidly, making it a challenge to keep up with new findings and advancements. We decided to take advantage of our day-to-day involvement with experienced clinical teams from proton therapy centers worldwide and gather and share information on the use of proton therapy in oncology.

We have compiled this information in a series of white papers reflecting the latest scientific and clinical advances in proton therapy. The information that follows is the result of our in-depth review of the latest articles published in key scientific journals.

We have undertaken this information-gathering exercise with honesty and ethics. While utmost care has been taken to ensure that the information contained in this publication is correct, unbiased and complete, the reader should be aware that articles have been selected and data interpreted. We encourage you to interpret these data carefully and exercise your own critical and scientific judgment.

The IBA team believes in the benefits of proton therapy for patients and society. This information exemplifies the extraordinary promise of proton therapy, and we hope you will join us in making it accessible to more patients.

We wish you a good reading,

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Breast cancer (BC) is now the most commonly diagnosed cancer in women.[1] Worldwide, an estimated 1.67 million BC cases were diagnosed in 2012, and among men and women combined, BC is now the second most commonly diagnosed cancer after lung cancer (1.82 million cases).[2] It is of paramount importance to be able to provide good treatment quality to women with BC.

A population-based comparison of women diagnosed between 1996 and 1998 found 5-year survival rates of 81% in Europe and 84% in the United States.[3] The 5-year relative survival of female patients with BC in the United States has increased steadily from 75.2% in 1975, 78.4% in 1985, 86.8% in 1995, and 90.6% in 2008.[4] Improvements in BC treatments have been instrumental in achieving this progress, and adjuvant radiation therapy is an important modality in many BC treatment regimens.[5,6]

WHOLE BREAST IRRADIATION AND PARTIAL BREAST IRRADIATION

Radical mastectomy was once the standard treatment for most BC patients, but radiotherapy (RT) offered the promise of breast conserving therapies. Twenty years ago it was shown that breast conserving surgery (BCS) followed by RT had equivalent efficacy as modified radical mastectomy as a loco-regional treatment for operable BC.[7] More recently it was shown that BCS combined with RT reduces the incidence of both in situ and invasive local recurrences by a factor of two and an overall lower risk of mastectomy in women with ductal carcinoma in situ (DCIS).[8] Moreover, a report by Bartelink et al. concluded, that a radiation boost after whole-breast irradiation (WBI) can improve local control with the largest absolute benefit in young patients, although it does increase the risk of moderate to severe fibrosis.[9]

Partial breast irradiation (PBI) refers to irradiation of a limited volume of breast tissue around the tumor bed that can be delivered by various radiation techniques such as brachytherapy (Interstitial or intracavity), intra-operative radiation machine, and external beam RT. Accelerated partial breast irradiation (APBI) delivers a larger than standard dose (≥2 Gray [Gy]) and thus shortens the overall duration of treatment. A recent meta-analysis assessed existing evidence in order to determine whether PBI/APBI is equivalent to or better than conventional or hypo-fractionated WBI after BCS for early-stage BC.[10] Compared to WBI, no differences were observed in PBI in terms of overall survival (OS), distant metastasis-free survival, nor loco-regional recurrence-free survival. The authors do note, however, that the ongoing trials tend to use APBI, and the results from these trials are awaited.

NODAL IRRADIATION

Indeed, most women with BC who undergo BCS receive WBI. A study published by Whelan et al. examined whether adding regional nodal irradiation to WBI improved outcomes in 1832 women with node-positive or high-risk node-negative BC who were treated with BCS followed by adjuvant systemic therapy.[11] Patients were randomized to receive either WBI plus regional nodal irradiation, which included internal mammary, supraclavicular, and axillary lymph nodes, or just WBI. At a median follow-up of 9.5 years, no significant difference was observed in OS between women receiving nodal irradiation, 82.8%, and those in the control group, 81.8% (hazard ratio [HR]=0.91; 95% confidence interval [CI], 0.72 to 1.13; P=0.38). However, women receiving nodal irradiation reported higher rates of disease-free survival (DFS), 82.0%, than those in the control group, 77.0% (HR = 0.76; 95% CI, 0.61 to 0.94; P=0.01).

At a median follow-up of 10.9 years, a study by Poortmans et al. showed that among 4004 patients with early-stage BC, irradiation of the regional nodes slightly improved OS, 82.3% versus 80.7%, DFS, 72.1% versus 69.1%, and BC mortality, 12.5% versus 14.4%, in patients who underwent nodal irradiation versus the control group, respectively.[12]

A randomized trial compared surgery and radiotherapy for positive axillary lymph nodes and showed that both axillary lymph node dissection and axillary RT provided excellent regional control for BC patients with a positive sentinel node biopsy.[13] Axillary RT reduces the risk of short term and long-term lymphedema as compared to axillary lymph node dissection.

For Locally Advanced BC, multimodal therapy comprises a systemic therapy using chemotherapy or targeted agents, combined with surgery, and RT, and here, RT can improve loco regional control.[14]

RADIATION-INDUCED ADVERSE EFFECTS

Adjuvant RT does improve tumor control and increases survival rates, but many patients, now survivors, experience late side effects as a result of having undergone such treatments. In fact, cardiac and pulmonary toxicities as well as second malignancies can, in a very real way, negatively impact these benefits, especially for young survivors.[15,16]

A meta-analysis reported a significant increased risk of second non-BC relative risk (RR) 1.12, including second cancer of the lung RR 1.39, esophagus RR 1.53 and second sarcomas RR 2.53 specifically at five years or more after BC treated with radiotherapy.[17] While intensity-modulated RT (IMRT) and volumetric modulated arc therapy (VMAT) have advantages in dose conformity compared to conventional 3-dimensional conformal RT (3DCRT), these newer techniques have a larger volume of normal tissue exposed to low dose radiation. Based on theoretical models, Hall et al[18] estimated that IMRT would almost double the incidence of second cancers compared to conventional 3DCRT. There is also an increased risk of second BC after internal mammary node (IMN) RT, a 7.2% increase versus 5.3% increase for patients with and without IMN RT, respectively, Courdi et al[19] reported in their retrospective study. However, a recent larger prospective trial reported that second ipsilateral or contralateral breast cancer occurred in 4.8% of the patients in the nodal irradiation versus 5.2% in the control group.[12]

Radiotherapy also linearly increases rates of major coronary events, 7.4% per Gy, with the mean dose to the heart; the increase starts within the first 5 years following radiotherapy and continues into the third decade after radiotherapy.[20] Cardiac toxicity is multifactorial and includes patient dependent risk factors, the therapies themselves, the anesthetic agents, etc. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) included 10,801 patients with BC in 17 randomized clinical trials. They found that after BCS, RT reduces the rate of disease recurrence by half and the mortality rate by a sixth. This analysis also demonstrated the increased risk of ischemic heart disease following RT for BC.[21]

Reviews by Taylor and colleagues acknowledge the risk of cardiac side effects related to BC RT and emphasize the need for oncologists to develop individual patient treatment plans based on absolute risks of radiation-related heart disease.[22] They noted a wide variance in heart doses administered to patients who participated in studies whose results were published between 2003 to 2013. The risk for an individual patient varies with the estimated cardiac radiation dose coupled with their own personal baseline risk of developing ischemic heart disease (in the absence of RT).

Currently, more patients with BC are becoming long-time survivors[23] and there is, therefore, an increased need to prevent long-term treatment toxicities. Treatments for BC continue to evolve, but in light of late treatment effects, assessment of the patient quality of life will need to continue to advance alongside development of these new treatments.[24]

Proton therapy (PT), because of its inherent physical property that most of its energy deposition occurs at a near-fixed point (termed the Bragg peak) and after which essentially no dose is deposited, has the ability to achieve full coverage of the target tissue and, simultaneously, optimal organ sparing. Therefore, PT has the potential to optimize tumor control while maximally sparing non-target tissue and reducing treatment morbidity. Taylor et al. reported a mean heart dose of 5.4 Gy (0.1 - 28.6 Gy) among 398 regimens in 149 studies from 28 countries.[25] Overall, they noted, PT delivered the lowest doses. Large trials are ongoing in order to investigate if protons' potential will translate to measurable clinical outcome benefits.[26]

PROTON THERAPY FOR PATIENTS WITH BREAST CANCER

A) OVERVIEW OF BENEFITS

PT is being increasingly used to treat patients with cancer, and as of May 2018, there were 63 PT Centers in operation in the world, 30 in operation in the United States, and 23 under construction or in development in the United States.[27] PT can deliver conformal therapy that can, compared to photon-based RT, reduce the dose to healthy tissue.[28] Today, BC is a highly curable disease. Patients are more likely to be long-term survivors and consequently experience late toxicity. For these patients, PT is a treatment option.

When using traditional photon and electron radiation methods, avoiding dose to the heart and lungs while

maintaining an effective dose to the target area is a challenge. However, because PT has an inherent rapid fall-off of dose distal to the target area, the dose to the target tissue can be optimized and the surrounding tissue can be spared. In practice, such reduction of the dose to the heart and lungs can reduce late cardiac and pulmonary toxic effects and, consequently, improve the quality of life for these patients.[29]

In this context, PT is well suited for patients with advanced disease, involvement of the IMNs,[30] pre-existing cardiac disease, and permanent implants or breast reconstruction.[31] Suitable indications would certainly include mastectomy patients and those requiring post-mastectomy RT (PMRT).[32]

B) DOSIMETRIC COMPARISONS

Protons have a dosimetric advantage over photons and spare organs at risk (OARs), e.g. heart, lung, and contralateral breast, from moderate and low doses of radiation. So, there may be potential benefits for patients with pre-existing cardiac or lung morbidities, young women, and women with genetic breast-cancer risk. Proton dosimetry is consistently better for locally advanced BC. It has been shown, for example, that PT can spare some cardiac substructures from high dose radiation, and the target coverage of PT is equivalent or better than RT. A systematic review conducted by Kammerer et al.[33] concluded that PT offered a better target coverage than RT, even compared with IMRT (including static or rotational IMRT or Tomotherapy). PT often decreased mean heart dose by a factor of 2 to 3, i.e., 1 Gy with PT versus 3 Gy with conventional 3D, and 6 Gy for IMRT. Lungs were better spared with PT than with RT, and with reduction in mean heart dose in BC irradiation, PT may reduce late cardio-vascular toxicity.

Mendenhall's group at the University of Florida investigated whether PT could improve the therapeutic ratio for patients with BC who are at risk for nodal disease.[34] They prepared 3-dimensional conformal photon + proton therapy (3DCX + PT), 3DCRT, and IMRT treatment plans for 10 patients with left sided BC. They determined that 3DCRT provided inferior regional node target coverage than either IMRT or 3DCX + PT. Furthermore, PT not only improved coverage of the regional lymph nodes, but it also decreased the dose to the heart, lung, and contralateral normal tissue.

Results of a prospective phase II study (NCT01365845) of radiation therapy for patients with stage II or III invasive adenocarcinoma of the breast requiring regional node irradiation published by Bradley et al.[35] showed that in a cohort including 18 patients (9 right- and 9 left-sided cancers) PT significantly improves cardiac dose. For patients with left-sided cancers, the median mean cardiac dose decreased from 5.9 Gy with conventional therapy to 0.6 Gy with PT. For all patients, ipsilateral lung V5 and V20 were significantly reduced, and these initial results show that PT improves both target coverage for the IMNs and the level 2 axilla.

Figure 1 illustrates the dose distribution for a typical left breast cancer with nodes and implants in Photon plan and in Proton (IMPT) plan.

Figure 2 presents the Dose Volume Histogram comparing CTV coverage and OAR doses of the Protons plan (dashed line) and the Photons plan (solid line) from Figure 1 (see page 6).

APBI using passive scattering proton beams spares significantly more normal tissue, including non-target breast and breast skin, than 3DCRT with photons according to a study published by Wang et al.[36] Their study included 11 patients who were sequentially treated with 3DCRT and APBI. The datasets from these patients were then compared with clinically treated 3DCRT photon plans, and calculations showed that the APBI plans provided a homogenous conformal treatment approach superior to that of the 3DCRT plans. The authors also considered the APBI plans were better able to accommodate motion and range uncertainties. Given similar target coverage and skin dose in the hypothetical toxicity dose region, the APBI plans showed a significant advantage for normal tissue sparing compared to the 3DCRT plans.

MacDonald and co-workers reported the delivery planning for PMRT for 11 patients using protons, partially wide tangent photon fields (PWTF), and photon/electron fields.[37] They achieved reasonable target volume coverage with PWTF and photon/electron fields, but they found that the PT plan was more homogeneous, realized superior coverage, and offered substantial sparing of heart and lung compared to the PWTF and photon/electron plans.

The left anterior descending (LAD) artery and the right coronary artery are particularly vulnerable to radiation, and PT is inherently better able to avoid OARs. Results of a comparative study of proton beam versus photon beam dose to the heart and LAD were reported by Lin et al.[38] That

study included ten patients with early stage left-sided BC. The patients were being treated with BCS and radiation, and they consented to participate in this prospective study on planning for deep inspiration breath hold (DIBH) IMRT and PBS and uniform scanning proton beam radiation therapies (PBT).

They found that both the PBS (0.011 Gy) and uniform scanning (0.009 Gy) proton plans resulted in a significantly lower mean heart dose compared to the IMRT (1.612 Gy) plan, and both PBT plans had lower minimum, maximum, and dose to 0.2 cm^3 of the LAD compared to the IMRT plan. These results could be important when considering late events such as coronary events involving the LAD.

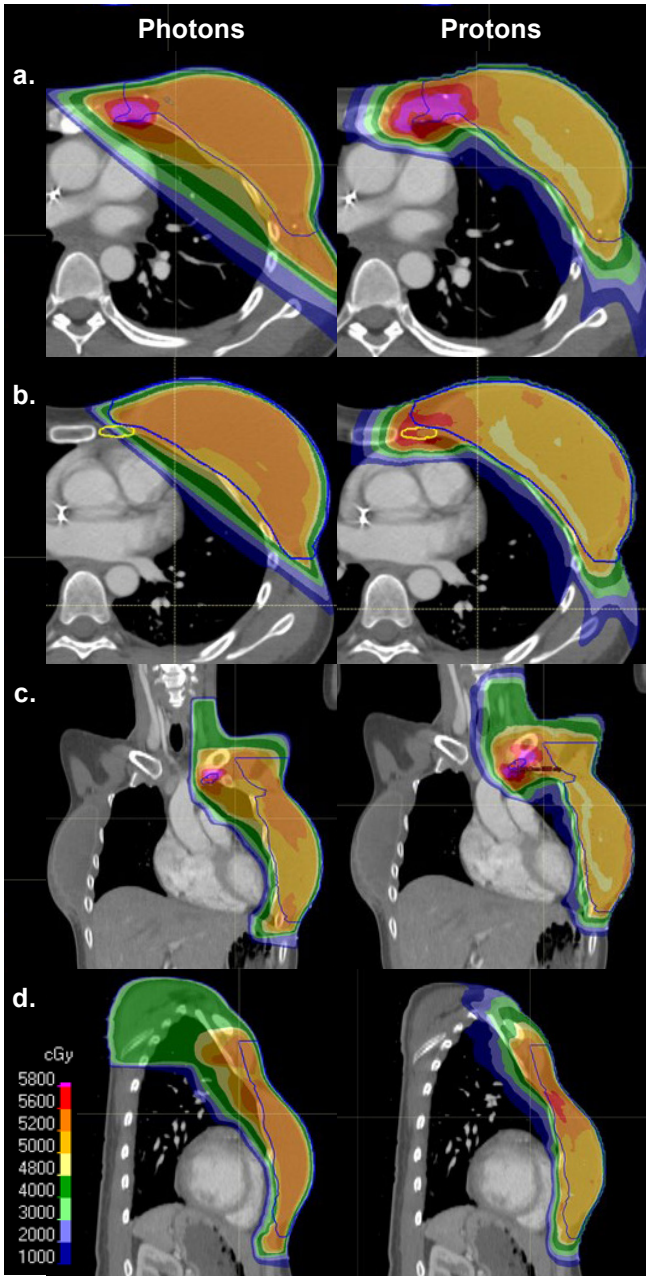


Figure 1: Isodose clouds for at the level of left internal mammary nodes boost (a) and lower internal mammary nodes region (b). Cumulative dose to Upper Supra-Clav was 45.0Gy (RBE) (c), cumulative dose to left breast (CTV_50.4) (d) was 50.4Gy (RBE) and cumulative dose to internal mammary nodes boost regions was 57.6Gy (RBE). In the photon plans (left column), target coverage to the internal mammary nodes and deep chestwall was restricted by the excessive dose to heart and lung.

Figures 1 & 2: compliments of Mark Pankuch PhD, Director of Medical Physics and Dosimetry, Northwestern Medical Chicago Proton Center.

Jimenez et al.[39] reported a treatment planning study for intensity modulated PT (IMPT) for PMRT of bilateral implant reconstructed breasts. The 5 women with BC included in this study also had bilateral breast implants which had either been implanted prior to treatment or following double mastectomy. The investigators created 10 plans each (5 left chest wall, 5 right chest wall) for IMPT, 3D conformal photon/electron, and conformal photon utilizing wide tangents. In these patients, the IMPT plan provided improved homogeneity to the chest wall and regional lymphatics and sparing of surrounding normal structures as compared to the photon/electron or photon plans.

A comparison of IMPT with IMRT was the subject of a preclinical study by Mast et al.[40] to determine if the proton technique combined with breath-hold would enable a dose reduction to the heart and LAD in left-sided BC RT. They prepared IMPT and IMRT plans with both breath-hold and free breathing for 20 patients who had undergone BCS. They were able to reduce the dose to the heart and LAD to almost zero in all patients with both IMPT plans. With the IMRT plans on the other hand, 9 patients received a mean dose to the LAD region exceeding 5 Gy, for 4 patients the dose was more than 10 Gy, and for 3 patients the mean heart dose was more than 2 Gy. The authors conclude that IMPT, even without breath-hold, reduces the dose to heart and LAD compared to photon therapy.

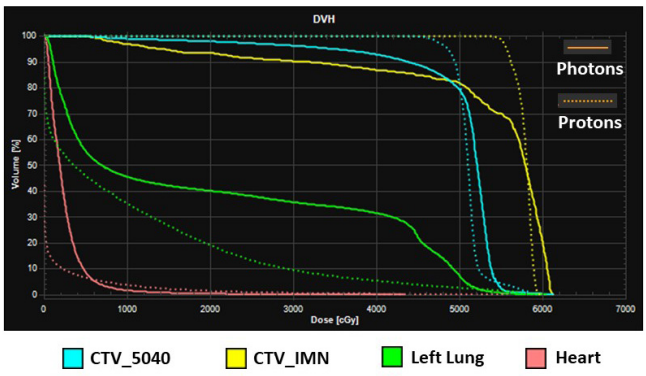


Figure 2: Dose Volume Histogram comparing CTV coverage and OAR doses of the Proton Plan (Dashed Line) and the Photon Plan (Solid Line). CTV coverage to the 50.4Gy target and the IMN target were limited by the heart and lung doses.

C) LITERATURE REVIEW – CLINICAL USE OF PROTON THERAPY FOR BREAST CANCER

Mehta's group at the University of Maryland Medical Center reviewed BC PT clinical outcomes and toxicity and found that PBT produces comparable or reduced toxicity rates compared to photon based radiation therapies.[41] They noted a decrease in the incidence of esophagitis and only rare reports of radiation pneumonitis or rib fractures in BC patients treated with PBT.

Chang et al. reported the results of a phase II, prospective study of proton beam accelerated partial breast irradiation (PB-APBI) in 30 such patients.[42] At a median follow-up of 59 months, all patients had survived and none had ipsilateral breast recurrence or regional or distant metastasis. Overall, reported toxicities were mild to moderate except for severe wet desquamation at 2 months in one patient that resolved at 6 months. The authors concluded that excellent disease control and tolerable skin toxicity can be achieved with PB-APBI in this patient group with early-stage BC.

Results of a multicenter, prospective clinical study of 3 dimensional conformal (3D) APBI were reported by Galland-Girodet et al.[43] Among 98 evaluable patients, 79 patients received photon-based 3D-APBI (60 with mixed photons and electrons, 19 with photons only) and 19 received PBT. Patients received 32 Gy in 8 fractions administered twice per day. Here, the local control rates were similar for each approach, but the investigators noted that PBT reduced the radiation dose to breast tissue lying outside the target volume, substantially decreased the proportion of non-target breast tissue and total breast tissue receiving half of the prescribed dose, and significantly spared the heart and lungs. Those patients receiving PT did experience higher rates of long-term skin toxicities, but the authors attribute this to the limited number of fields used. They point out that advanced proton scanning techniques and IMPT can improve conformity near the target, reduce skin dose, and produce less skin toxicity than 3D-APBI.

Strom et al.[44] argue that using protons for APBI is a good fit, and they put the long term results of the above mentioned study by Galland-Girodet et al. at Massachusetts General Hospital and that by Bush et al.[45] at Loma Linda University into perspective. In the Massachusetts General Hospital study, skin toxicities were more common for the PT group: 69% versus 16% of the patients reported telangiectasia, 54% versus 22% reported pigmentation changes, and 62% versus 18% reported other late skin toxicities in the PT versus RT groups, respectively. In contrast, there were no cases of grade 3 or higher acute skin reactions reported in the Loma Linda University study, and only 7 patients had grade 1 telangiectasia. Strom and Ovalle attribute the differences in toxicities observed in the two studies to the dose/fraction schemes, plan margins, and the number of beams. In the Massachusetts General Hospital study, patients received 32 Gy over 4 days using 2 daily fractions compared to the Loma Linda University study where patients received 40 Gy spread over 10 days with only 1 treatment per day. The 4 Gy dose fractions were identical in each study, but the Loma Linda University study spread a higher total dose over a longer time period. As for planning volumes, the Massachusetts General Hospital study used a 2 cm - 3 cm expansion on the excision cavity to develop the planning target volume, whereas the Loma Linda University study used a 1 cm expansion. Finally, Loma Linda University used up to 4 incident beams, and multiple fields were treated at every fraction on all patients. Consequently, their patients developed only mild to moderate radiation dermatitis and no cases of grade 3 or higher skin toxicity.

A PT study by MacDonald et al.[32] reported acute toxicities and feasibility of proton delivery for 12 women. Of these 12 patients, 11 patients were treated for left-sided BC, 5 of whom had permanent implants, and one patient was treated for right-sided BC, and this patient had bilateral implants. All patients received a dose of 50.4 Gy to the chest wall and 45 to 50.4 Gy to the regional lymphatics. The maximum reported skin toxicity was grade 2, and the maximum fatigue was grade 3.

A study by Cuaron et al.[46] treated 26 patients with PT following BCS. At a median follow-up of 15 months, there were no grade 3 adverse early or late events, 12 patients reported acute Grade 2 dermatitis, six developed moist desquamation, 12 reported late grade 1 hyperpigmentation, one reported telangiectasia, and three reported fibrosis. No cases of pneumonitis, cardiac toxicity, or rib fractures were reported, and 23 patients had an excellent or good cosmetic outcome.

Verma et al.[47] reported outcomes of 91 patients with locally advanced BC who were treated with adjuvant PT targeting the intact breast/chest wall and comprehensive regional nodes. Grades 1, 2, and 3 dermatitis occurred in 23%, 72%, and 5%, respectively. Eight percent required

treatment breaks owing to dermatitis. Grades 1, 2, and 3 esophagitis developed in 31%, 33%, and 0% patients. The authors concluded, that PBT displayed acceptable toxicity in the setting of comprehensive regional nodal irradiation.
Initial results of an ongoing study of conventionally fractionated breast/chest wall PT showed that about one fourth of the patients developed grade 1 dermatitis, and three fourths developed grade 2 dermatitis.[34] The number of patients developing skin toxicities using the double scattering technique were at least equivalent to, if not less than, skin toxicity rates for RT,[44] and future studies using pencil beam scanning (PBS) could offer the potential to further decrease skin dose.

Mutter et al.[48] reported an initial experience of 12 postmastectomy patients of breast expanders with metallic ports who received IMPT. The study showed that IMPT is feasible in this group of patients and associated with favorable clinical target volume coverage and normal tissue sparing. The maximum physician-assessed acute radiation dermatitis was grade 3 in 1 patient, grade 2 in 5 patients, and grade 1 in 6 patients.

Depauw et al.[49] have reported an approach to PMRT that offers a solution to reduce skin, pulmonary, and cardiac toxicities. Using proton pencil beam scanning (PBS) with intensity modulation, they are able to achieve complete target coverage of the chest wall and all nodal regions while reducing the dose to the heart and lungs. The study, conducted at the Massachusetts General Hospital, used an in-house proton planning system that treated the dose to the chest wall skin as a distinct optimization objective. They were able to achieve target coverage and organ sparing comparable to passive scattering proton beam treatments, and they also achieved better nodal coverage and cardiac sparing compared to conventional photon/electron beam treatments. The overall treatment time was shorter than these other techniques, as well. The accuracy of the skin dose calculation was within ±2%, and the treatment was well able to accommodate setup uncertainties and patient breathing motion.

PT spares heart, lung, and contralateral breast while allowing effective target coverage according to study results published by Cuaron et al.[50] In this single center study, 30 patients with non-metastatic BC and no history of prior radiation were treated with PT. Patients received a median 50.4 Gy (relative biological effectiveness [RBE]) dose over 5 weeks, and the target volumes included the breast/chest wall and regional lymph nodes including the internal mammary lymph nodes. Among 28 patients who were followed-up for more than 3 months, 20 reported grade 2 dermatitis, 8 experienced moist desquamation, 8 reported grade 2 esophagitis, and 1 patient had grade 3 reconstructive complications.

Researchers from Loma Linda University Medical Center, led by Principal Investigator Dr. David Bush, reported 5-year results with cosmetic outcome for the ongoing phase II trial of lumpectomy and partial breast PT for early stage BC.[45] One hundred patients with invasive non-lobular carcinoma underwent partial mastectomy followed by postoperative PBT to the surgical bed (40 Gy in 10 fractions), and at a median follow-up of 5 years, in-breast recurrence-free survival rate was 97%. Mild to moderate radiation dermatitis (graded as 1 or 2) was reported for 62% of the patients, but no cases of grade 3 or higher skin toxicity were reported. This clinical study (NCT00614172) is ongoing.

PT may prove cost effective for select patients,[51,52] and society must decide the value of decreased side effects of treatment and/or increased tumor control. Inclusion of the management of side effects into the cost analysis may offset the initial higher cost of proton delivery.

A recent review by Verma et al.[53] analyzed available data concerning the cost-effectiveness of PBT. Such cost analyses are a public health priority, and results of such analyses will likely change in step with increased access for patients with cancer to PBT. Current data are promising for PT. Results show that for BC, costs were higher for PT than for traditional photon RT, but for certain indications such as left-sided cancers at high risk of cardiac toxicity, costs were favorable in comparison to brachytherapy for proton-APBI.

Shannon MacDonald and coworkers at Massachusetts General Hospital acknowledge that PT is currently a costly modality, but it does have potential, particularly with respect to reducing the cardiac dose for patients undergoing breast irradiation.[54] They analyzed the cost-effectiveness of patients receiving breast irradiation with an eye towards finding dosimetric scenarios where PT would be cost effective compared to RT. Their results show that PT is cost effective in women with cardiac risk factors ≥1 in situations where the RT plan cannot achieve a mean heart dose <5 Gy.

Three separate cost analysis studies found that no scenarios were cost saving at a willingness to pay (WTP) < $0, and no scenarios in women without risk factors were cost-effective considering a WTP of $100,000 per quality adjusted life year (QALY).[55] Cost-effectiveness with a WTP of $100,000 per QALY was realized at doses of MHD 7Gy and above for 40-year-old women, at ≥6 Gy for 50-year-old women, and ≥6 Gy for women 60-year-old with at least one cardiac RF. Cost-effectiveness with a WTP of $50,000 per QALY was observed in a particular case, women with at least one cardiac risk factor who were 50 years old and a mean heart dose of 10Gy.

In assessing cost effectiveness, both the cost of treatment as well as the cost of side effect management need to be considered. For example, heart failure can effect a heavy burden on healthcare resources, and studies in the United States have estimated costs of $1000 to $25000 for heart failure inpatient admission, medical costs for treating heart failure ranging from $750 to $1626 per person per year, and a total inpatient cost for Medicare beneficiaries discharged after admission for heart failure at approximately $12,719 per year.[56,57]

A review of cost-utility assessments in oncology can be found in a paper published in the Journal of Clinical Oncology in 2000 by Earle et al.[58] Indeed, one has to assess cost effectiveness by disease, but overall, notably, the number of fractions influence the cost, and reducing the number from 25 down to 5 can exact a significant savings.

D) ONGOING CLINICAL TRIALS

In the world of evidence-based medicine, clinical trials are crucial in order to demonstrate the superiority of one treatment with respect to others. A list of ongoing clinical trials in PT for BC are presented in Table 1, and several of these studies are described below.

RADCOMP (NCT02603341) is a randomized pragmatic trial funded by the U.S. Patient-Centered Research Outcomes Institute and the National Cancer Institute. It aims to assess the effectiveness of proton vs. photon therapy in reducing major cardiovascular events (MCE) for patients with locally advanced BC whose treatment includes the IMN. The primary hypothesis is that PT will reduce the 10-year MCE rate after radiation from 6.3% to 3.8%, It plans to enroll 1716 patients in over 30 proton centers coming from over 70 participating radiation treatment centers across the United States. They plan both passive and active follow-up techniques, and enrolled patients will be followed longitudinally for cardiovascular morbidity and mortality, health-related quality of life, and cancer control. Such long term follow-up is needed to enable investigators to determine if PT can, in a meaningful way, reduce radiation-induced cardiovascular toxicities for patients with BC.[26] Key inclusion criteria are invasive mammary carcinoma (ductal, lobular or other) of the breast; non-metastatic or locally recurrent; mastectomy or lumpectomy with any type of axillary surgery or axillary sampling; left or right sided; proceeding with comprehensive nodal radiation with inclusion of IMN. Key exclusion criteria are prior RT to ipsilateral breast or chest wall, prior contralateral RT eligible; scleroderma. RADCOMP physics created learning network, and this engages clinicians and physicists. The RADCOMP Breast and Heart Atlas is available for download.[59] RADCOMP is sponsored by the Abramson Cancer Center of the University of Pennsylvania and is open to US-European collaboration.

Initial results have been reported for twelve patients enrolled in an ongoing phase II clinical study (NCT01340495) to investigate the use of proton radiation therapy for patients with invasive breast carcinoma following mastectomy that opened in August 2011 at the Massachusetts General Hospital.[32,60] Patients with this condition require radiation therapy, so a goal of this study was to determine the feasibility of using proton radiation for patients with unfavorable cardiac anatomy or implants that would make standard planning technically difficult. Enrolled patients receive 45-50.4 Gy relative biological effectiveness (RBE) to the chest wall and 45-50.5 Gy (RBE) once daily, 5 days per week, for approximately 5 1/2 weeks. At 8 weeks following the completion of proton radiation therapy, the maximum reported skin toxicity was grade 2 according to the CTCAE, and the maximum reported CTCAE fatigue was grade 3.

The Proton Collaborative Group is sponsoring two studies utilizing PT for patients with BC. The phase II BRE007-12 study (NCT01766297) will assess events of freedom from ipsilateral breast recurrence occurrences in patients with early stage who are administered partial breast proton radiation therapy limited to the region of the tumor. The investigators point out that studies show many tumors recur in or adjacent to the original tumor site. This study seeks to answer the question of whether radiation to the whole breast is necessary or justified, and if limiting radiation to the area of the original tumor might reduce acute and long-term skin and organ toxicities. With the phase II/III BRE008-12 study (NCT01758445), the Proton Collaborative

Group plans to determine the rates of acute and long-term adverse events of postoperative PT for complex logo-regional irradiation in women with loco-regionally advanced BC. In particular, this study includes longitudinal long-term (10 and 15 years) follow-up in order to assess the incidence of cardiac mortality and second malignant neoplasms following PT in these patients.

Cardiac and pulmonary toxicities of PT for BC are being investigated in two studies sponsored by the University of Florida. One of these is a prospective phase I pilot study of early markers of radiation-induced cardiac injury in patients with left-sided BC receiving photon or PT (NCT02199366). This observational study seeks to determine if there are changes in heart function following the completion of radiation therapy for BC as measured by cardiac magnetic resonance imaging (MRI). In addition, investigators will assess cardiac side effects from radiation treatment, compare cardiac MRI changes according to radiation technique, and assess quality of life questionnaires. The other study (NCT02725840) opened in March 2016 and aims to better identify BC patients at high risk for experiencing severe pulmonary toxicity, and who might therefore require medical intervention. Patients will be assigned to either of two active comparator study arms: PBT or x-ray-based radiation therapy. The investigators point out that despite advanced radiation techniques for dose conformality to minimize exposure of the highly sensitive lung, 14% of BC patients treated with radiation develop clinical pulmonary toxicity, and 4% experience high grade clinical toxicity. The investigators aim to provide a means of identifying toxicity early and thereafter tailor treatment and/or early intervention to the individual patient.

The phase II APBI PT study (NCT01839838) will examine the feasibility, side effects, and clinical efficacy of using PT on only the tumor bed of 57 patients being treated for stage IA-IIA BC after surgical removal of just the malignancy. This study, sponsored by the Abramson Center, aims to establish the effects of this type of therapy compared to traditional radiation as well as whole breast therapies.

The utility of imaging biomarkers in detecting subclinical cardiotoxicity across a spectrum of radiation doses to the heart will be determined in an Abramson Center sponsored study (NCT02769299). The investigators hypothesize that radiation therapy induces early, subclinical cardiovascular injury, as evidenced by cardiomyocyte inflammation and necrosis, and deteriorating cardiovascular function. This observational study will follow 50 patients with BC, lung cancer, or mediastinal lymphomas who are being treated with photon or proton therapies.

Another study (NCT00599989) sponsored by the Abramson Cancer Center gives patients with early stage BC who are undergoing breast conservation therapy access to APBI therapy in a controlled trial. Target enrolment is 100 patients, and the aim is to collect prospective data on acute and late toxicity and disease recurrence.

A phase II study was initiated to determine the efficacy and toxicity of PT when used to deliver partial breast RT (NCT01310530). Sponsored by Loma Linda University, this study aims to recruit 150 patients with early stage BC following surgical removal and determine the recurrence rates and side-effects partial breast PT.

Assessing cosmesis and toxicity of partial breast irradiation using proton beam irradiation is the primary objective of a clinical research study sponsored by the M.D. Anderson Cancer Center (NCT01245712). Here, the goal is to find out if a 1-week course of partial breast irradiation using PT causes fewer and/or less severe side effects than a longer course of radiation therapy. At 1-year, the anticipated 100 enrolled patients will self-report cosmesis scores using the Breast Cancer Treatment Outcomes Scale.

Pencil beam scanning proton radiotherapy (PBS) is the focus of a study sponsored by the Mayo Clinic (NCT02783690). This phase II randomized controlled trial plans to enroll 82 patients requiring regional nodal irradiation following mastectomy to determine the safety of 15 fraction as opposed to 25 fraction PBS.

The Mayo clinic is also sponsoring a study designed to determine the safety and efficacy of a novel 3 fraction daily dosing regimen for APBI in 168 patients with early invasive and noninvasive BCs (NCT02453737). This phase II study will utilize three techniques recognized as standard options for the delivery of APBI:

- Brachytherapy APBI
- 3D-Conformal Radiation Therapy (photon) APBI
- Proton APBI

Currently, there is no level 1 evidence to support that any one technique is superior or inferior to the others.

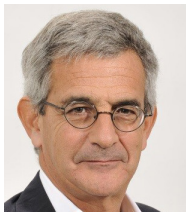
Table 1: Ongoing clinical trials (1/2)

Title	Conditions	Type Phases	Sponsor	Outcome measures	Duration	No.Patients	NCT no
Prophylactic Irradiation to the Contralateral Breast for BRCA Mutation Carriers Undergoing Treatment for Breast Cancer	Stage I-III BC undergoing BCT with breast irradiation	Interventional Phase II	Assaf-Harofeh Medical Center	Rate of contralateral breast cancer in carrier patients that received prophylactic radiation to the contralateral breast compared with carrier patients that did not receive that treatment.	2008-2023	240	NCT00496288
Pilot Study of Proton Radiation Therapy for Invasive Breast Carcinoma Following Mastectomy	Invasive BC following mastectomy	Interventional	Massachusetts General Hospital	Safety/ Efficacy	2011-2017	96	NCT01340495
Phase II Protocol of Proton Therapy for Partial Breast Irradiation in Early Stage Breast Cancer	Early-Stage Breast Cancer	Interventional Phase II	Proton Collaborative Group	Safety/ Efficacy	2013-2030	42	NCT01766297
Phase II Study of Postoperative, Cardiac-Sparing Proton Radiotherapy for Patients with Stage II/III Loco-Regional, Non-Metastatic Breast Cancer Requiring Whole Breast or Chest Wall Irradiation with Lymph Node Irradiation	Stage II/III loco-regionally advanced BC	Interventional Phase II	Proton Collaborative Group	Safety/ Efficacy	2013-2022	220	NCT01758445
Prospective Pilot Study of Early Markers of Radiation-Induced Cardiac Injury in Patients with Left-Sided Breast Cancer Receiving Photon or Proton Therapy	Breast cancer	Observational Phase I	University of Florida	Cardiac function; cardiac side effects; quality of life	2014-2020	16	NCT02199366
Early Markers of Subclinical Pulmonary Vascular Radiation Toxicity in Breast Cancer	Radiation injury, BC	Interventional	University of Florida	Identify differences between the treatment modalities, proton versus X-ray	2016-2021	55	NCT02725840
Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial	Non-metastatic BC	Interventional Phase III	Abramson Cancer Center of the University of Pennsylvania	Effectiveness of PT vs. photon therapy; disease control; quality of life; dosimetry; cardiac toxicity	2016-2060	1720	NCT02603341
A Feasibility and Phase II Trial of Accelerated Partial Breast Irradiation Using Proton Therapy for Women with Stage Ia-IIa Breast Cancer	Stage Ia-IIa Breast Cancer	Interventional Phase II	GT insertion required: Abramson Cancer Center of the University of Pennsylvania	Adverse events	2013-2024	57	NCT01839838
Cardiotoxicity of Radiation Therapy (CTRT)	Breast Cancer; Lung Cancer; Mediastinal Lymphomas	Observational	Abramson Cancer Center of the University of Pennsylvania	Cardiotoxicity	2015-2017	50	NCT02769299
Accelerated Partial Breast Irradiation	Breast Cancer	Interventional	Abramson Cancer Center of the University of Pennsylvania	Toxicity	2005-2010	100	NCT00599989
Phase 2 Trial of Partial Breast Proton Therapy for Early Stage Breast Cancer with Low and Intermediate Risk Factors	Early-Stage Breast Cancer	Interventional Phase II	Loma Linda University	Safety/ Efficacy Rates of recurrence; DFS; complication rate	2011-2017	150	NCT01310530
Assessing the Cosmesis and Toxicity of Partial Breast Irradiation Using Proton Beam Irradiation	Breast cancer	Interventional	M.D. Anderson Cancer Center	Safety/ Efficacy Cosmesis rate	2010-2017	100	NCT01245712

Table 1: Ongoing clinical trials (2/2)

Title	Conditions	Type Phases	Sponsor	Outcome measures	Duration	No.Patients	NCT no
MC1631: A Randomized Trial of 15 Fraction vs 25 Fraction Pencil Beam Scanning Proton Radiotherapy After Mastectomy in Patients Requiring Regional Nodal Irradiation	Breast cancer	Interventional Phase II	Mayo Clinic	Complication rate	2015-2018	82	NCT02783690
A Phase II Study of Accelerated 3 Fraction Photon and Proton Partial Breast External Beam Radiotherapy and Partial Breast Brachytherapy for Early Invasive and Noninvasive Breast Cancer	Breast cancer	Interventional Phase II	Mayo Clinic	Cosmesis	2015-2018	168	NCT02453737
Proton Therapy for Lymph Nodes in Breast Cancer (BR01)	Breast cancer – peripheral lymph nodes	Interventional Phase I	University of Florida	Volume of Heart Receiving ≥ 5 Gy	2012-2019	18	NCT01365845
Proton Therapy for Early Stage Breast Cancer	Early stage Breast cancer	Interventional Phase II	Loma Linda University	Survival and recurrence	2004-2019	150	NCT00614172
Hypofractionated Radiotherapy After Breast Conserving Surgery (MC1635)	Breast cancer	Interventional Phase II	Mayo Clinic	Complication rate	2017-2023	82	NCT03339934

THE EXPERT'S PERSPECTIVE



Dr Alain Fourquet,
Head of Department of Radiation Oncology (2006-2017)
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Dr Alain Fourquet is a senior Radiation Oncologist at the Institut Curie in Paris, France, and former Head of the Department of Radiation Oncology (2006-2017). His research focuses on the multidisciplinary management of patients with breast cancer, breast cancer in young women, ductal carcinoma in situ of the breast, and the concurrent delivery of systemic therapies and radiotherapy in breast cancer. He has contributed to improve and develop translational research programs in proton therapy, at the Institut Curie Proton Therapy Center which has operated a proton therapy facility since 1991.

He has written numerous book chapters and didactic papers, and contributed to more than 260 publications on breast cancer in peer-reviewed journals.

THE PRESENT

When asked about his views on current radiotherapy for breast cancer, Dr Fourquet pointed out that the results of recent prospective randomized trials showed that radiotherapy of the breast or chest wall and regional nodes significantly decreased the rates of distant metastases, in patients who received adjuvant systemic chemotherapy and endocrine therapy.

Dr Fourquet stated that the use of modern radiotherapy delivery techniques allow to achieve excellent target volumes coverages in almost all clinical situations, particularly when treating the breast or chest wall along with the regional lymph nodes. "These techniques, using photons and electrons," he explained, "can achieve excellent long term cosmetic results in patients treated with breast-conserving surgery with limited toxicity to the skin and breast normal tissue. However, long term cardiac and pulmonary toxicities can occur in these patients. Since breast cancer survival rates have constantly improved, long term toxicities remain a challenge."

As for the question of the possible role of proton therapy in present clinical practice, Dr Fourquet commented "dosimetric comparisons of proton therapy and photon therapy in breast cancer always show a similar quality of target volumes coverage, with a substantial advantage of protons in sparing organs at risk such as heart, lungs, and contralateral breast cancer." He continued "clinical experience in the use of PT in breast cancer is still very limited. Results were reported on small series of patients, usually retrospective, treated with various proton therapy techniques (double scattering, pencil beam scattering), totalizing roughly 200 patients, with short follow-ups." He emphasized "these studies suggest that treating breast cancer with protons is feasible, that the acute side effects might be slightly increased with protons when compared to photons, and that short-term sequelae are not increased. Prospective trials have started to include patients."

Dr Fourquet further commented that at present, the cost of proton therapy is a serious limitation to its widespread use for patients with breast cancer. Though the number of proton therapy center increases continuously worldwide, the cost of investment and operation is still much higher than that of photon therapy.

THE FUTURE

According to Dr Fourquet, the dosimetric advantage of using proton in breast cancer radiotherapy looks particularly attractive in patients who are treated on the breast or chest wall, and lymph nodes areas. "Potentially, proton could be chosen rather than photons in specific situations where a clear benefit would be expected in sparing as much as possible the organs at risk," Dr Fourquet specified, "that would include: 1) patients with pre-existing cardiac or pulmonary illnesses in whom heart or lung irradiation, even at low doses, should be avoided; 2) very young patients or carriers of breast cancer predisposing germ-line mutations in whom even low doses to the contralateral breast could dramatically increase the risk of a new contralateral breast cancer; and 3) all potential difficult clinical cases, where particular patients' anatomy would degrade the quality of target coverage in order to spare the organs at risk."

Dr Fourquet believes that the results of the clinical studies should be available in several years and will help to assess the tolerance of proton therapy – "they should provide criteria to adequately select patients, based on the identified benefits of proton and the identified risks of photons, and thus improve the efficiency of radiotherapy of breast cancer."

In addition, Dr Fourquet expects that the increase number of new proton machines available and the technological improvements should allow to progressively decrease the costs and thus allow a larger number of selected patients to have access and benefit from proton therapy.

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NOTES

NOTES

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