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Original Research Article

PTCOG international survey of practice patterns and trends in utilization of proton therapy for breast cancer

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ABSTRACT

Purpose/objectives: The indications, techniques, and extent to which proton beam therapy (PBT) is employed for breast cancer are unknown. We seek to determine PBT utilization for breast cancer.

Materials/methods: The Particle Therapy Co-Operative Group (PTCOG) Breast Subcommittee developed an IRB-approved 29-question survey and sent it to breast cancer radiation oncologists at all active PBT centers worldwide in June 2023. Descriptive statistics were used to summarize responses, and comparisons by continent were performed using Fisher's exact tests.

Results: Of 79 surveys distributed, 28 recipients submitted responses (35 % response rate) representing fifteen U.S., 8 European, and 5 Asian centers (continent response rate 50 %, 38 %, and 18 %, respectively). Overall, 93 % reported treating breast cancer patients with PBT; 13 (50 %) have treated ≥100 breast cancer patients at their center since opening. Most (89 %) have pencil beam scanning technology. Nearly half (46 %) use moderate hypofractionation (15–20 fractions) for regional nodal irradiation and 42 % conventional fractionation (25–30 fractions). More European centers prefer hypofractionation (88 %) vs. Asian (50 %) and U.S. (21 %) centers ($p = 0.003$). Common patient selection methods were practitioner determination/patient preference ($n = 16$) and comparative plan evaluation ($n = 15$). U.S. centers reported the most experience with breast PBT, with 71 % having treated ≥100 breast cancer patients vs. 38 % in Europe and none in Asia ($p = 0.001$). Of respondent centers, 39 % enrolled ≥75 % of breast PBT patients on a research study.

Conclusion: Utilization, patient selection methods, and dose-fractionation approaches for breast cancer PBT vary worldwide. These survey data serve as a benchmark from which successor surveys can provide insight on practice pattern evolution.

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Introduction

Proton beam therapy (PBT) technology has become increasingly available over the past two decades with expansion of proton centers across the globe. Over the same period, PBT technology has advanced, leading to greater ability to treat more complex disease types and tumor volumes. Innovations including pencil beam scanning technology, more standard incorporation of on-board CT-based image guidance, improved robust optimization tools, and enhanced motion management capabilities have allowed for the expansion of PBT application, including to breast cancer, in which target coverage can be optimized while heart and lung dose are reduced [1–5]. Multi-field optimized PBT, or intensity-modulated proton therapy (IMPT), is another recent development that allows for more precise control of PBT spot dose delivery, including to the skin, allowing for excess skin dose reduction and mitigating the degree of radiation dermatitis previously observed with older PBT delivery methods – an advancement that holds particular value for breast radiotherapy [6]. With emerging clinical data worldwide, this international survey of PBT centers was developed to determine the prevailing application of PBT for breast cancer. The Particle Therapy Cooperative Group Breast Subcommittee sought to establish a benchmark of the current state of international utilization of PBT for breast cancer and associated relevant patient selection and treatment delivery parameters across all active PBT centers worldwide.

Methods and materials

A survey instrument was developed by the Particle Therapy Co-Operative Group (PTCOG) Breast Subcommittee comprised of members representing countries in North America, Europe, and Asia. Study approval was obtained from the Western Institutional Review Board. The survey included 29 questions spanning 5 primary topics on 1) overall utilization of PBT for breast cancer, 2) technology, 3) patient selection criteria, 4) dose-fractionation regimens, and 5) clinical trial enrollment. The majority of questions were multiple choice in nature (n = 23); open-ended questions (n = 6) were primarily used to collect patient volume data (Supp. Fig. 1). We identified all active PBT centers worldwide as of February 2023 from the PTCOG Facilities in Operation webpage, and representative breast cancer radiation oncologists were identified from each institution. Prior to wide distribution to all recipients, the survey was tested by PTCOG Breast Subcommittee leadership to ensure quality integrity. Surveys were then delivered electronically via a SurveyMonkey email link.

Statistical analysis

Descriptive statistics, including frequencies and percents, were performed to summarize responses. Comparisons by continent relied on Fisher's exact tests. All statistical analyses were performed using R statistical software (v4.2.3; R Core Team 2023). Statistical significance was taken at the $p < 0.05$ level and did not account for multiplicity.

Results

Seventy-nine active PBT centers in 19 countries were identified. Of 79 surveys distributed to representatives at each institution, 28 recipients submitted responses, corresponding with a 35 % response rate. Respondent institutions represented 10 countries across 3 continents (Supp. Table 1). Fifteen (54 %) participating institutions were in North America (all North American centers were located in the U.S.), 8 (29 %) in Europe, and 5 (18 %) in Asia. The response rate amongst North American, European, and Asian centers was 50 %, 38 %, and 18 %, respectively, with representative countries including the U.S. (n = 15), England (n = 2), Spain (n = 2), the Netherlands (n = 2), Denmark (n = 1), Italy (n = 1), China (n = 1), India (n = 1), Japan (n = 1), South Korea (n = 1), and Taiwan (n = 1) (Fig. 1). Over half of respondents (n = 18, 64 %) self-classified as academic institutions, 14 % (n = 4) hospital-based nonacademic centers, and 21 % (n = 6) private practice or

Fig. 1. Distribution of respondent proton centers worldwide by institution type. Blue = academic institution. Red = Private practice/other. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

other type of facility.

Respondent institutions reported the year their center became operational and the year they treated their first breast cancer patient. The total number of operational PBT centers (Fig. 2a) and the total number of operational centers treating breast cancer patients (Fig. 2b) increased amongst respondent institutions from 2006 to 2023. The number of operational respondent PBT centers in the U.S. increased from 2 to 15, in Europe from 0 to 8, and in Asia from 0 to 5 over that time period.

At the time of this survey study, 26 of the 28 responding centers (93 %) were actively treating breast cancer patients with PBT. U.S. centers reported treating more breast cancer patients with PBT than European and Asian counterparts (Supp. Table 2, Fig. 3a and b). Twenty-three of 28 (82 %) responding centers reported having both photon and PBT capabilities. Among these centers, 12 (57 %) treated 1–9 %, 4 (19 %) treated 10–24 %, and 5 (24 %) treated > 25 % of their breast cancer patients with PBT.

The most common indication for PBT was breast/chest wall with regional nodal irradiation (RNI) (Fig. 4). Sixteen centers (57 %) reported that > 50 % of breast cancer patients received PBT for breast/chest wall and RNI; 61 % of centers reported that ≥75 % of patients who received RNI had internal mammary node (IMN) irradiation. For breast/chest wall with RNI, twelve centers (43 %) preferred moderate hypofractionation (defined as 15–20 fractions), 11 (39 %) conventional fractionation (defined as 25–30 fractions), and 5 centers (18 %) did not routinely use PBT for RNI. Hypofractionation was the preferred RNI regimen in most European centers (88 %) vs. 50 % in Asia and 21 % in the U.S. ($p = 0.003$; Supp Table 2). Of centers treating breast cancer patients with PBT, 75 % of centers reported treating breast cancer patients also with PBT in the setting of reirradiation. Partial breast irradiation (PBI) was the least common indication for PBT, with nearly half (n = 13, 46 %) reporting that no patients received PBT for PBI. PBT with palliative intent was rarely used for breast cancer, with centers reporting either treating none (14/25, 56 %) or 1–9 % (10/25, 40 %) of their breast cancer patients in this setting.

All patient selection methods being utilized at responding institutions were reported and included practitioner determination/patient preference (n = 16), comparative plan evaluation (n = 15), institutional guidelines (n = 11), and DVH modeling (n = 9). In the U.S. and in Asia, the most commonly used patient selection approaches included comparative plan evaluation and practitioner determination/patient preference (73 % and 67 % of respondent U.S. centers, respectively; 40 % and 80 % of respondent Asian centers, respectively); by contrast, in Europe, DVH modeling and institutional guidelines were the

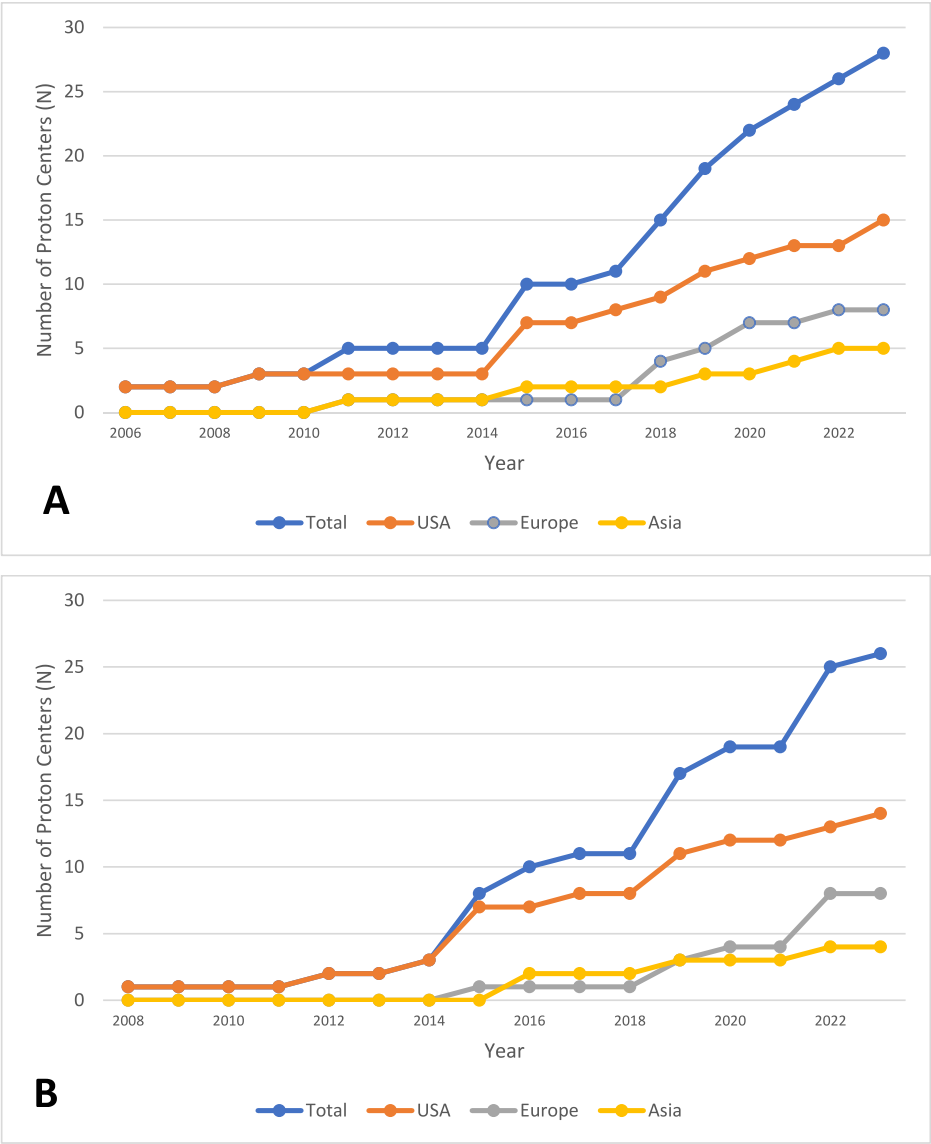

Fig. 2. Annual number of respondent proton centers that were operational (A) and treating breast cancer patients (B).

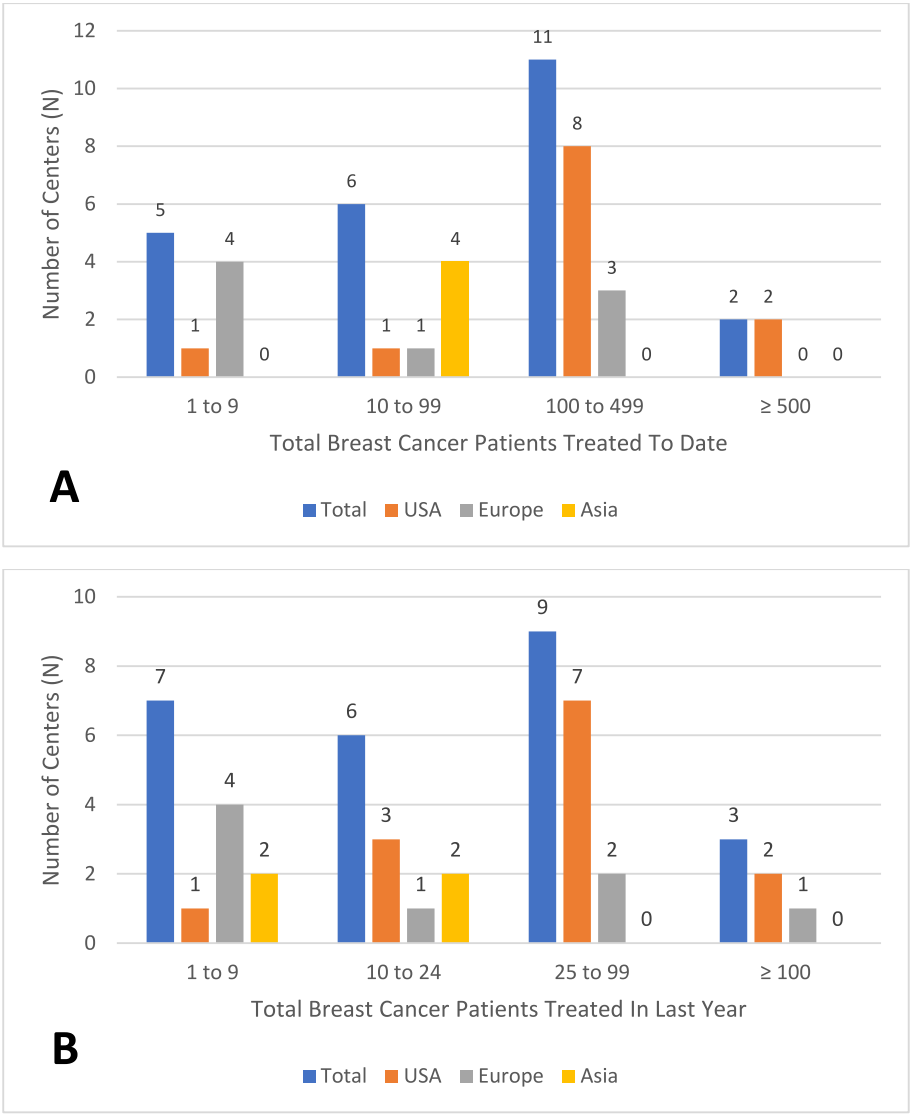

Fig. 3. Number of breast cancer patients treated with proton therapy at respondent centers to date (A) and in the last year (B).

predominant methods (50 % and 38 % of respondent European centers, respectively). In 39 % of centers, ≥75 % of breast cancer patients treated with PBT were enrolled on a research study; half (50 %) of centers enrolled ≥50 % of breast PBT patients on a research study. Physician referral (58 %) and self-referral (42 %) were common methods by which patients accessed PBT facilities.

The technology available at the various responding centers is summarized in Table 1. Most centers (n = 25, 89 %) reported primarily using pencil beam scanning to treat breast cancer patients. The majority of centers (n = 24, 86 %) had CT imaging for image guidance, with the most common techniques used for daily image guidance for breast treatment including cone beam CT/CT on rails (n = 18, 64 %) and/or kV (n = 20, 71 %). Ten centers (36 %) used Eclipse (Varian Medical Systems, Inc., Palo Alto, CA, USA) for their treatment planning system, and 17 centers (61 %) used RayStation (RaySearch Laboratories, Stockholm, Sweden).

Nine of 12 respondents (75 %) noted that their willingness to use PBT for breast cancer patient treatment would differ with increased machine time availability. The availability of CT image guidance and pencil beam scanning technology impacted willingness to treat breast cancer patients with PBT for 5 of 8 and 2 of 6 respondents, respectively. Lack of insurance authorization was reported as a major barrier to breast cancer treatment across all continents, with 5 centers (18 %) reporting that PBT is ultimately not delivered in over half of breast cancers patients for whom the provider would consider PBT for this reason (Asia, n = 2; Europe, n = 2; U.S., n = 1).

Discussion

This is the first multi-institutional survey of PBT treatment patterns for breast cancer patients. Our study shows increased use of PBT over time for breast cancer among responding operational centers. This data is consistent with 10-year survey data (2012–2021) from the National Association for Proton Therapy (NAPT), which showed a 15.6-fold increase in the annual number of breast cancer patients receiving PBT in 37 U.S. centers over this period [7]. There has been a marked increase in the total number of active proton centers worldwide. As of May 2024, there are 45 active PBT centers in the U.S., 38 centers in Asia, and 32 centers in Europe and Russia [8]. Thus, the number of patients being treated for breast cancer and other indications is expected to continue to rise with increased access to proton therapy facilities and greater emphasis on limiting excess dose to non-target tissues to reduce the risk of late effects of cancer therapy.

RNI was the most common indication for PBT among responding centers, with over half of centers reporting >50 % of breast cancer patients receiving RNI when receiving PBT. Dosimetric studies have shown

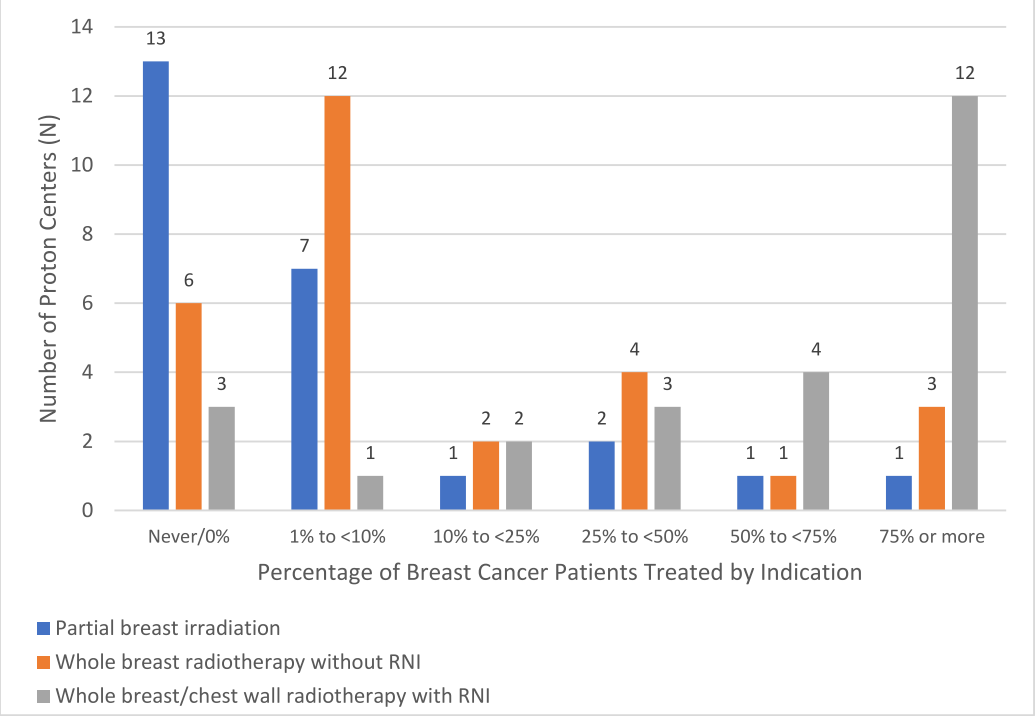

Fig. 4. Percentage of breast cancer patients treated by indication at respondent centers. RNI = regional nodal irradiation.

that PBT post-mastectomy radiotherapy (PMRT) reduces dose to the heart, lungs, and esophagus without compromising target volume coverage [3,5,9,10]. Prospective clinical trials from the University of Florida and Massachusetts General Hospital showed that PBT demonstrated significantly lower heart and lung dose compared with 3DCRT using either photon-electron matched fields or partially wide tangents [4,11,12]. A recent *meta*-analysis including 1452 patients reported that the most common severe adverse outcome after scanning PBT to the whole breast or chest wall with or without the regional lymph nodes was radiation dermatitis, which occurred in 6 % of patients, with other severe outcomes occurring rarely (≤1% of patients) [13]. There are currently 3 ongoing randomized trials comparing PBT with photon radiotherapy to the whole breast or chest wall with or without RNI inclusion. The three trials are based in the USA (NCT02603341), the UK (ISRCTN14220944), and Denmark (NCT04291378) (Table 2). The decision to use PBT for RNI may be influenced by the laterality of disease (right vs. left) and inclusion of the internal mammary chain in the treatment volume or not. The impact these factors have on modality selection and PBT utilization patterns will be addressed in future surveys.

Breast reirradiation is also a common indication for PBT, with 75 % of centers using PBT in the setting of prior in-field radiotherapy. In a study of the two PBT facilities operating in Korea (National Cancer Center and Samsung Medical Center) including 5398 patients receiving PBT, reirradiation was commonly associated with the receipt of PBT compared to other types of radiation (12.8 % vs. 4.7 %, $p < 0.001$) [14]. In a multi-institutional prospective registry of 50 breast cancer patients who underwent proton reirradiation between 2011 and 2016, one-year locoregional recurrence-free survival was 93 % and any (acute or late) grade 3 adverse events were observed in 16 % of patients [15]. Several institutional retrospective studies have further shown excellent local control and low rates of high-grade toxicities in patients receiving breast reirradiation with PBT [16–18]. There is one clinical trial listed in the registry of the National Institutes of Health (NIH) studying reirradiation using PBT for breast cancer patients (NCT05313191) in three settings: partial breast reirradiation for early, favorable, in-breast recurrence or new primary; 2) comprehensive reirradiation to the breast/chest wall and regional lymph nodes for high risk breast cancer recurrence; and 3) any other reirradiation for breast cancer recurrence using PBS PBT. The primary outcome of the study is the rate of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade 3 or greater acute and late treatment effects within two years of reirradiation completion.

The optimal dose/fractionation for PBT in patients undergoing RNI is not known. Twelve centers (42.9 %) reported using moderate hypofractionation, 11 centers (39 %) reported using conventional fractionation, and 5 centers did not respond (18 %). When comparing between continents, our survey showed that hypofractionation was the preferred PBT RNI regimen in most European centers (88 %) vs. 50 % in Asia and 21 % in the U.S. ($p = 0.003$). This slower uptake of proton hypofractionation in the U.S. parallels a similar trend of photon hypofractionation. A National Cancer Database analysis showed that the use of hypofractionated whole breast irradiation in the U.S. increased from 0.7 % in 2004 to 15.6 % in 2013 [19]. In a similar period of time, hypofractionation for whole breast irradiation was already widely adopted in the U.K. (80 % of centers) [20]. The body of data exploring moderate hypofractionation in the delivery of photon RNI is growing. A single center, phase 3 study from China of 820 patients who underwent mastectomy without reconstruction demonstrated that hypofractionated PMRT (43.5 Gy in 15 fractions) was not inferior to conventionally fractionated PMRT (50 Gy in 25 fractions) in 5-year locoregional recurrence [21]. There were also no significant differences in acute and late toxicities between the two groups excepting less grade 3 acute skin toxicity in patients receiving hypofractionation. The multicenter FABREC trial reported on 385 evaluable patients who underwent mastectomy with immediate tissue expander or implant reconstruction and were randomized to conventionally fractionated vs. hypofractionated PMRT. While the primary endpoint of improvement in the Physical Well-Being (PWB) domain of FACT-B at 6 months was not different between the two arms, fewer hours off from work were required for those patients receiving hypofractionated PMRT [22]. The rate of chest wall toxicity and disease control were comparable between the two arms. The Alliance A221505 RT CHARM trial randomized patients who underwent mastectomy with breast reconstruction to comprehensive PMRT using 50 Gy in 25 fractions or 42.5 Gy in 2.66 Gy, with a goal of determining if

Table 1
Technology available at respondent proton centers.

	Number of Proton Centers (N, %)
Proton technology	
Passive scatter/double scatter	6 (21.4)
Uniform scanning	2 (7.1)
Pencil beam scanning	25 (89.3)
Proton technology used for majority of breast cancer patients	
Passive scatter/double scatter	3 (10.7)
Pencil beam scanning	25 (89.3)
CT image guidance available (on board cone beam CT or CT on rails)	
Yes	24 (85.7)
No	4 (14.3)
IGRT used for breast PBT treatment delivery*	
Cone beam CT/CT on rails	18 (64.3)
kV	20 (71.4)
Surface guidance	9 (32.1)
Motion management (DIBH)	3 (10.7)
Willingness to treat breast cancer patients with PBT differ with availability of:	
Pencil beam scanning technology/IMPT	
Yes	2 (7.1)
No	4 (14.3)
NA	22 (78.6)
CT image guidance (on board cone beam CT or CT on rails)	
Yes	5 (17.9)
No	3 (10.7)
NA	20 (71.4)
Machine time	
Yes	9 (32.1)
No	3 (10.7)
NA	16 (57.1)
TPS used for breast cancer PBT	
Eclipse	9 (32.1)
Eclipse, RayStation	1 (3.6)
RayStation	16 (57.1)
PRTP-M	1 (3.6)
NA	1 (3.6)
Photon therapy available	
Yes	23 (82.1)
No	5 (17.9)

CT = computed tomography; IGRT = image-guided radiotherapy; PBT = proton therapy; kV (kilovoltage); DIBH = deep inspiratory breath hold; IMPT = intensity-modulated proton therapy; TPS = treatment planning system.

the rate of reconstruction complications at 24 months after radiation was noninferior using a hypofractionated approach; results of this trial are forthcoming. In addition, results from the DBCG Skagen trial 1 (NCT02384733) randomizing 2900 high-risk breast cancer patients between 50 Gy in 25 fractions vs. 40 Gy in 15 fractions are awaited; all patients received RNI (with or without reconstruction), and the primary endpoint is 3-year lymphedema.

The use of moderate hypofractionation when delivering RNI with PBT also remains under investigation. A randomized phase 2 trial from the Mayo Clinic investigating conventional versus moderate hypofractionation in 88 patients undergoing proton PMRT showed no difference in protocol-defined complication rates (n = 6, 15 % conventional fractionation vs. n = 8, 20 % hypofractionation, p = 0.27)) [23]. However, noninferiority of hypofractionation could not be established, potentially in part due to the trial sample size. Of note, all complications occurred in patients with immediate expander or implant-based reconstruction, and the absolute rate of some late grade 1–2 adverse events (breast and arm edema, non-cardiac chest pain), along with late grade 3 breast infection, were numerically higher in the hypofractionation arm. COMPRO is a currently enrolling phase III, multicenter, noninferiority trial from the Proton Collaborative Group (NCT05856773) that will randomize 276 patients receiving proton RNI after definitive surgery using a moderately hypofractionated regimen (40.05 Gy in 15 fractions) or conventional fractionation (50.0–50.4 Gy in 25 to 28 fractions). The primary endpoint is grade ≥3 treatment-related skin and soft tissue toxicities.

Table 2
Ongoing randomized proton vs. photon trials in breast cancer patients.

Study Name	Study Years	Estimated Enrollment	Study Arms	Primary Endpoint
DBCG Skagen 2 [NCT04291378] Denmark	2020–37	1502	PBT vs. photon 50 Gy/25 fx	Ischaemic and valvular heart disease at 10 years
RadComp [NCT02603341*] USA	2016–32	1278	PBT vs. photon 50 Gy/25 fx	Major cardiovascular events at 10 years
PARABLE [ISRCTN14220944] UK	2022–30	192	Scanning PBT vs. photon IMRT 40 Gy/15 fx	Mean heart dose, patient-reported normal tissue toxicity in the breast at 2 years

PBT = proton therapy; fx = fractions; IMRT = intensity-modulated proton therapy.

Additional data and experience will continue to guide optimal breast cancer patient selection for PBT. In our survey, the most commonly used methods for determining PBT application include practitioner determination, patient preference, and comparative plan evaluation. Institutional guidelines and DVH modeling strategies are available and/or used at a minority of centers. Efforts are underway to develop and apply prognostic models that will provide a more objective approach to breast cancer patient selection for PBT. Boersma and colleagues in the Netherlands reported on a novel clinical model in which breast cancer patients with an estimated 2 % or greater absolute lower risk of acute coronary events based on mean heart dose with PBT vs. photon therapy will be approved for PBT reimbursement [24]. The ongoing UK PARABLE trial (ISRCTN14220944) randomizes breast cancer patients receiving radiotherapy to receive photon therapy or PBT who have been determined to have an estimated 2 % or higher lifetime risk of radiation-induced late major cardiac events, or approximately a 3 Gy or higher mean heart dose. In the phase III DBCG Skagen Trial 2 (NCT04291378), patients with early breast cancer are randomized to PBT vs. photon therapy if the mean heart dose would be ≥4 Gy and/or ipsilateral lung V17/20 Gy ≥37 % using a photon-based treatment plan [24]. The results of these studies will be informative for future baseline measures that may be used for more uniform evaluation of candidacy for PBT and to identify patients who may gain meaningful clinical benefit from this modality.

The majority of respondent centers began treatments after 2015, when most centers were already being developed with modern pencil beam scanning proton therapy, which is also reflected in the nearly 90 % reported availability of this technology among participating survey institutions. The majority of breast cancer patients are also treated with this technology. Similarly, access to CT image guidance is incorporated as standard technology in newer PBT centers and does impact practitioner willingness to use PBT for breast cancer radiotherapy. Interfraction soft tissue and positional variability disproportionately impacts large-field breast radiotherapy, introducing opportunities for set-up error and soft tissue change during the radiotherapy course, which results in a less robust plan. The ability to ensure accurate treatment delivery allows for minimum necessary setup uncertainty margins,

maximizing PBT's normal tissue sparing potential. With more consistent availability of sophisticated PBT technology in more centers, high quality treatment delivery and the ability to treat complex breast cancer plans will be possible. The most significant barriers to the application of PBT for more breast cancer patients were access to ample machine time and insurance coverage, issues that will be alleviated with the development of new PBT centers worldwide and continued evidence generation.

A limitation of this study is that not all centers responded due to the voluntary survey method. It is possible that the indications, techniques, and extent to which PBT is used for breast cancer may vary between respondents and non-respondents, potentially impacting the generalizability. However, the 35.4 % response rate is consistent with the average rate for online surveys [25–28], and we had strong representation from North America, Europe and Asia, with at least one center from 11 of 19 countries with PBT responding. There were a number of "NA," or not applicable, responses to several survey questions, primarily attributed to 1) lack of access to the technology in question or 2) lack of experience in the treatment approach of reference. This illustrates the evolving landscape and heterogeneity of current PBT technology availability and utilization worldwide and underlies the importance of establishing a baseline of the breast PBT landscape from which future study can be conducted.

Conclusion

As the number of breast cancer patients receiving PBT continues to increase internationally, there is significant heterogeneity in patient selection and PBT technique. Comparative plans and DVH modeling are commonly employed to aid in patient selection, and the most common indications are RNI and reirradiation. In the first survey of international practice patterns on the use of PBT for breast cancer, we are able to establish a benchmark on the current global state of PBT utilization in this patient population. Successor surveys will provide insight into the evolution of practice patterns as additional data and experience emerge using PBT in the treatment of breast cancer.

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CRediT authorship contribution statement

J. Isabelle Choi: Conceptualization, Data curation, Writing – original draft, Formal analysis, Funding acquisition, Investigation, Writing – review & editing, Supervision. **Camille Hardy-Abeloos:** Data curation, Writing – original draft, Formal analysis, Writing – review & editing. **Alicia Lozano:** Data curation, Formal analysis, Writing – review & editing. **Alexandra Hanlon:** Data curation, Formal analysis, Writing – review & editing. **Carlos Vargas:** Writing – review & editing. **John H. Maduro:** Writing – review & editing. **Julie Bradley:** Writing – review & editing. **Birgitte Offersen:** Writing – review & editing. **Bruce Haffty:** Writing – review & editing. **Mark Pankuch:** Writing – review & editing. **Richard Amos:** Writing – review & editing. **Nalee Kim:** Writing – review & editing. **Shannon M. MacDonald:** Writing – review & editing. **Youlia Kirova:** Writing – review & editing. **Robert W. Mutter:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S. M.M. reports travel reimbursement and speaking engagements with IBA and ICOTEC. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100847.

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