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# Pre-operative partial breast irradiation: revolutionizing radiation treatment for women with early stage breast cancer

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## Abstract

Partial breast irradiation (PBI) has been increasingly accepted as a suitable component of breast conservation in the management of patients with early stage breast cancer, however the majority of existing studies have focused on the use of adjuvant or intra-operative techniques. Several early stage studies have more recently shown that PBI can be safely used in the pre-operative setting. Early data show similar local control without evidence of increased toxicity or worsening cosmesis, as compared to postoperative PBI or standard whole breast irradiation. While long term data are still maturing, pre-operative accelerated PBI (PAPBI) offers a number of possible clinical advantages including reducing the treatment field and increasing the number of patients eligible for PBI, identifying biomarkers of response to radiation, and improving the rates of breast conservation and treatment compliance. This review discusses key concepts and controversies



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surrounding PBI as it has increasingly been adopted in the US, Canada, and Europe, and introduces the concepts and early studies of PAPBI. In addition, we summarize ongoing clinical trials investigating PAPBI, review clinical benefits and challenges associated with PAPBI versus postoperative PBI, and discuss ongoing limitations as well as next generation technologies important to the implementation of PAPBI in the management of patients with early-stage localized breast cancer.

### Keywords

Partial breast irradiation (PBI); early stage breast cancer; radiation therapy; pre-operative radiation therapy; stereotactic body radiation therapy (SBRT)

## Introduction

The management of early stage breast cancers has shifted significantly in the past decade. Thus far, this has been driven by advances in the availability and application of molecular and genomic testing to guide systemic treatment decision making. However, local therapies namely surgery and radiation therapy, remain the backbone of breast conservation therapy. For most patients with early stage breast cancers undergoing breast conservation, adjuvant whole breast radiation therapy (WBRT) using a modestly hypofractionated treatment regimen remains the standard of care (1-3).

However, in the last few years, there have been a number of new advances made in the local management of early stage breast cancer. These are driven by and rely on the advances in imaging, image guidance and treatment planning across the field of radiation oncology, leading to the development of novel concepts of management of early stage breast cancer including the use of accelerated partial breast irradiation (APBI). This entails the use of hypofractionated regimens similar to the hypofractionated regimens of WBRT, or the use of shorter regimens delivered over one to ten fractions. Data from the last decade has demonstrated the safe implementation of PBI as compared to WBRT in the postoperative setting. Many phase III randomized studies have largely shown that PBI is associated with good cosmetic and toxicity outcomes, without compromising local failure rates when compared to WBRT (4-7).

More recently, multiple early stage, proof-of-concept trials are investigating the use of PBI in the pre-operative setting (8-10). This review introduces the history and development of PBI and reviews the clinical benefits and challenges associated with pre-operative APBI (PAPBI) therapy. We also discuss the advent of next generation technologies such as magnetic resonance (MR) guided radiation therapy (RT) and Cyberknife in PAPBI as well as challenges that still remain facing more widespread adoption of PAPBI. A summary of several ongoing or recently accrued PAPBI and postoperative PBI studies is provided in Table 1.

## Definition and adaptation of APBI

APBI refers to the delivery of hyperfractionated, modestly hypofractionated, or extremely hypofractionated radiation therapy to the tumor-involved part of the breast as a part of breast conservation therapy. The concept of PBI developed from modern pathological analysis, which have shown that in most cases, even amongst patients who required localized re-excisions after lumpectomy, residual disease in the breast was typically limited to a margin of <10 mm around the lumpectomy cavity (11). Thus, in patients who underwent sufficient definitive resection, it was rationalized that postoperative RT could be reasonably limited to just the resection cavity plus a moderate margin without missing microscopic tumor.

Over the last several years, APBI has become more widely accepted and is now commonly utilized at most academic centers in the US and Canada. Most studies on APBI to date have shown promising local control rates as compared with WBRT, albeit most studies still have a comparably shorter follow up duration (5,7,12). APBI can be delivered via various techniques including brachytherapy, both 3D conformal and intensity modulated external beam radiation therapy (EBRT), stereotactic body radiation therapy (SBRT), or intraoperative radiation therapy (IORT). Because of the significantly fewer fractions employed, higher doses per fraction are typically employed for PBI as compared to conventionally fractionated techniques, but it is delivered over a significantly smaller area. With the exception of IORT, which is delivered in a single fraction, PBI is most often delivered over the course of a short regiment of 5–10 fractions over 1–2 weeks to a total dose ranging from 15–40 Gy. As PBI is still an emerging treatment concept, studies have used variable dosing and fractionation regimens, hence resulting in a range of acceptable variations that is largely institution dependent.

## New interest in and advantages of PAPBI

Nevertheless, only a minority of women undergoing breast conservation in the US, Canada and Europe are treated with PBI. Limitations to widespread adoption have been attributed to concerns for an increased risk of local recurrence, poorer cosmesis and increased dose heterogeneity to the postoperative lumpectomy cavity, particularly in patients with larger tumors/cavities or small breast volume (13,14). These concerns persist even though multiple phase III studies have shown otherwise (4,6,15).

A theoretical advantage of using pre-operative therapy is the possibility of avoiding some of these toxicities that could be associated with postoperative therapy. Typically, a smaller volume could be treated (gross tumor versus post-operative tumor bed) and consequently, the area receiving the highest dose in PAPBI would be largely, if not completely, removed during lumpectomy. This would mitigate concerns regarding fibrosis or necrosis of the breast tissue in the treatment field.

Pre-operative radiation therapy has been shown to have advantages in the management of other solid tumors including cancers of the rectum, esophagus, and sarcomas. However, until very recently, pre-operative therapy has had a very limited role in the clinical management of localized breast cancer outside of clinical trials, being primarily reserved for patients with

unresectable tumors despite neoadjuvant chemotherapy. In such cases, patients are offered the option of pre-operative radiation therapy with the goal achieving resectability at the time of surgery.

The hesitancy to use pre-operative RT is in part driven by historical data suggesting that there may be increased toxicity with pre-operative RT, even though most of these studies were conducted in the 1980s to early 2000s. Such studies utilized older radiation therapy techniques rather than modern 3D-based or intensity-modulated treatment planning technology. Many of these studies also used concurrent pre-operative chemotherapy, likely further increasing the likelihood of treatment-related toxicity and rates of subsequent surgical complications (16-18).

In fact, modern PAPBI studies have been implemented safely in a number of Phase I/II clinical studies. These trials, done comparatively or as an alternative to postoperative RT for patients with early stage breast cancer, typically included patients who fulfill the ASTRO APBI appropriate use guidelines. While the data is not yet mature, early reports from these studies do not appear to show significantly increased risk of toxicity or evidence of association with increased postoperative complications (19-21). In fact, some advocates of PAPBI find that there is in fact more uncertainty associated with postoperative RT, particularly when a boost is needed. In some institutions, cosmetic tissue rearrangement with oncoplastic reconstruction may take place following tumor resection at the time of lumpectomy, which can complicate treatment planning, lead to increased treatment volumes, and result in unnecessary toxicity (22-24). The use of pre-operative RT obviates this concern.

Another potential benefit of PAPBI is that it can increase the number of patients who are candidates for PBI as the total breast volumes irradiated in the pre-operative setting is likely significantly less as compared to the postoperative setting. This is because post-operative treatment fields must encompass the entire surgical bed, which is significantly larger in most cases than the gross tumor. Nichols *et al.* estimated that the pre-operative versus postoperative treatment volume APBI for 41 early stage breast cancer patients using pre-operative and postoperative imaging, showing that radiating the pre-operative tumor rather than the tumor bed can significant reduce the treatment volume (19). Women with larger tumor to breast size ratio who would otherwise not have been candidates for adjuvant PBI may now be candidates for PAPBI. Given the significantly reduced treatment times with comparably or potentially better toxicity outcomes, this is beneficial both for the patient and the healthcare system at large.

Finally, a generally cited added benefit of PAPBI is treatment compliance. Surprisingly, epidemiological analysis shows that 18% of women in the US who are eligible for adjuvant RT did not receive post-lumpectomy treatment. The cause of attrition in this setting is likely multi-factorial, but it obviously has an adverse impact on local control and survival (25). In addition to shortening the duration for RT, by moving PBI to the pre-operative setting, we may see significant improvement in treatment compliance.

## Treatment planning techniques in the era of PAPBI and SBRT

The earliest studies of PAPBI, such as a Phase II multi-institutional study in the Netherlands testing the toxicity and cosmetic outcome after 40 Gy in 10 daily fractions, did not require advanced treatment planning intensity-modulated radiation therapy (IMRT)/SBRT or the use of magnetic resonance imaging (MRI). This study permitted the use of 3-dimensional conformal radiotherapy (3-DCRT) for treatment planning, but the protocol specified increased clinical target volume (CTV) to planning tumor volume (PTV) expansion to 2.5 cm (21). Nevertheless, even with these large margins, the mean PTV to ipsilateral breast ratio was still less than 15%. Thus, there remains a significant reduction in treated breast volume as compared to WBRT (21). An interim report from Van de Leij on this study including 70 patients showed that 100% of patients had good to excellent cosmesis at 3 years with minimal treatment related and postoperative toxicity and only 2 local recurrences at a median follow up of 23 months.

More modern studies of PAPBI using advanced treatment planning have led to reduced treatment fields, which consequently also provided opportunities for dose escalation. Specifically, studies have shown that PAPBI can be done safely in as little as a single fraction. For example, Horton *et al.*, reported early results of a single institutional Phase I dose-finding study of single fraction PAPBI (20). This study included a total of 17 patients with T1 disease greater than 1 cm from the skin surface and used MRI for planning. Prescription was to 15 Gy ×1 using IMRT. While median follow up is only 23 months, cosmesis was rated as good or excellent in all patients without any evidence of early recurrence. While the use of MRI in treatment planning is fairly novel, breast MRI has become increasingly recognized as important in pre-surgical staging and treatment response assessment for patients with breast cancer.

Subsequently, Yoo *et al.* and Blitzblau *et al.* performed a dose escalation trial, testing up to 21 Gy in a single fraction in an additional 32 patients (26,27). They required the use of prone MRI and prone CT for planning, using the biopsy clip as a fiducial for daily cone beam CT verification of treatment setup. The study authors emphasized the importance of having MRI for planning as CTs were found to be insufficient for visualizing tumors and/or underestimated tumor sizes. These authors also pointed out the importance of being able to administer this using EBRT. In contrast to brachytherapy or IORT, EBRT does not require specialized equipment and comparably, less operator dependent expertise, thus making it more widely available to patients.

The conclusion from the above studies in the context of more extensive data with PAPBI is that while advanced treatment planning and delivery (i.e., IMRT or availability of MRI simulation) is not always required, they offer increased target precision. This reduces the margin expansion needed for treatment set up variation and therefore, may improve cosmesis and reduce risk of toxicity. Furthermore, the advent of new image-guided radiotherapy (IGRT) technologies incorporating intra-fractional IGRT and magnetic resonance-based linear accelerators (MR-LINACS) has the potential to even further improve the accuracy and precision of treatment planning.

## Application of modern IGRT and novel treatment modalities to PAPBI

Another form of IGRT incorporates intrafractional, fiducial tracking using the Cyberknife (Accuray, Palo Alto CA). Most of the experience with using Cyberknife and fiducial tracking for PBI has been in the postoperative setting (28). Initial reports were made in 2011 by the Swedish Medical Center in Seattle and Winthrop University Hospital of a combined analysis of 47 patients treated with either 10 fractions twice daily (BID) or 5 fractions daily to a dose of 25–36 Gy (29). In this particular study, as a part of treatment planning for APBI, gold fiducial markers were placed at the time of surgery or post-operatively by radiation oncologists. The target CTV included a minimally 2 mm PTV expansion. Additional work at University of Texas South Western (UTSW) reported the outcomes of 75 patients treated from 2010–2015 utilizing gold fiducials and synchrony real time tracking. In this case, no CTV to PTV margin was used so CTV = PTV (10). In both analyses, cosmesis was excellent.

Dosimetrically, using Cyberknife as opposed to 3D EBRT appears to result in a significantly lower dose to the organs at risk while maintaining conformal target coverage, as reported by comparative studies by UTSW and Fox Chase Medical Center (30,31). Implementing the use of Cyberknife fiducial tracking may be more challenging logistically with PAPBI, as fiducials would not be available. However, there is likely an opportunity for collaboration with diagnostic radiology so that fiducials could be placed at the time of US-guided biopsy or in a subsequent encounter, similar to the process currently being utilized for fiducial tracking in patients with prostate cancer. Alternatively, as has been done by the Swedish Medical Center/Winthrop Study, the treating radiation oncologist could also place these fiducials at the time of CT simulation. As noted above, there is potentially less margin for error when localizing to = fiducials placed in the tumor mass as compared to fiducials placed in the healing postoperative cavity at the time of or after surgery, as there may be movement of the fiducial markers in the tumor bed/cavity during wound healing.

In addition to Cyberknife, newer advanced image guidance technologies are being investigated. The Gammapod, currently being tested at the University of Maryland, is similar in concept to the Gammaknife and uses Cobalt-60 (32). The patients are loaded onto the “pod” in a standing position and are then transitioned into a prone position with a vacuum assisted breast cup that can interlock into the couch and maintain the position of the breast once the patient is prone. The patient can then be imaged using a CT or MRI simulator with the breast cup in place in a separate location. Then, the patient can be returned to the unit for treatment. Another technology that is being developed is a stereotactic unit called the Mammoknife which is a self-shielded device dedicated to the treatment of patients with breast cancer, shielding the rest of the patient’s body to scatter radiation exposure. A prototype has been available since 2010, but it is pending final FDA testing and approval with likely implementation in the next few years (15).

## Molecular and correlative studies

An added value of PAPBI therapy is that it can theoretically provide an opportunity to assess treatment response. Tissue sampling before radiation can provide an opportunity to identify

biomarkers that prognosticate patient outcomes akin to that already used to assess for decisions regarding pre-operative chemotherapy. A response assessment after pre-operative RT would also offer an opportunity to guide the use of adjuvant therapy. In addition, this allows for tissue sampling that can be used for biomarker studies of radiation response. Such studies have the potential to guide the development of future predictive or prognostic biomarkers and shed light on the biology of how breast cancer cells respond to radiation. For example, Horton *et al.* showed that Luminal subtype cells derived from patients following PAPBI at the time of lumpectomy showed a much higher gene expression response profile to radiation than Her2+ or basal cell types (20). They postulated that PAPBI may complement the use of neoadjuvant chemotherapy since the opposite is typically observed.

Another notable PAPBI study is that by Nichols *et al.*, who reported on the use of fractionated SBRT delivered to a dose of 38.5 Gy in 3.85 Gy twice daily fractions at least 3 weeks prior to lumpectomy. Importantly, they were able to report findings from the H&E samples of the patients' surgical specimen. The rates of pathologic complete response (pCR) observed was observed in 4 out of the 27 treated patients. No local failures were reported after 3 years of follow up (19). The interpretation of the low percentage of pCR patients is limited by the short delay between RT and lumpectomy. Given that it is well-established that radiation-mediated cell death is a late process that occurs over weeks to months, it is certainly possible that with longer time between RT and surgery, a greater rate of pCR would be observed.

The role of PAPBI in affecting tumor response is being better addressed in more modern studies including one Canadian pilot study by Tiberi *et al.* They observed a good pathological response in 8/10 study participants with median of 3% residual cellularity and pCR of 50% (8). Indeed a recent trial from the Netherlands (ABLATIVE), which is a single-arm prospective study of 36 patients who underwent single fraction PAPBI (15 Gy to CTV and 20 Gy to GTV) 6–8 months prior to lumpectomy, showed a promising rate of 42% of both pCR and radiographic complete response (67% with both) (9). More advanced genomics and molecular immunology studies of tumors after PAPBI have not yet been reported, but would add important knowledge to the literature regarding differential tumor response to radiation therapy and potentially identify new molecular biomarkers to guide clinical management.

## Future directions and considerations

Perhaps a radical proposal, but there is a possibility here for the investigation of how PAPBI can play a role either in conjunction with, complementary to or in lieu of preoperative systemic or endocrine therapy for patients with early stage hormone receptor (HR) positive breast cancer. For example, it is well-established that patients with HR positive disease are less likely to respond to preoperative chemotherapy. Thus, for these patients, preoperative RT may be a good alternative. Additionally, PAPBI has some potential advantages when compared to neoadjuvant chemotherapy. Comparatively, pre-operative RT is likely faster, more convenient, and less morbid. Most importantly, in nearly all patients with early stage breast cancer regardless of whether systemic therapy would be recommended, RT remains a

central component of breast conservation and significantly reduces local-regional recurrence on the order of two-thirds.

Finally, PAPBI can lead to pathologic downstaging, and thereby potentially reduce the overuse of systemic therapy, which can be morbid or associated with late toxicities. In patients with a dramatic response to RT, chemotherapy may no longer be recommended after definitive surgery for some patients, even though they may have been recommended chemotherapy based on pre-operative staging.

Finally, some have raised the idea of being able to use non-invasive biomarkers in conjunction with imaging to potentially select candidates who may be able to avoid lumpectomy after pre-operative therapy. It is certainly possible that adding PAPBI to pre-operative systemic therapy may further improve the rates of pCR such that there may a possibility of avoiding surgery in certain carefully-selected patient populations. There are certainly good precedents for this paradigm in other solid malignancies where neoadjuvant chemoradiation was a part of a standard of care paradigm that required surgical resection but over time chemoradiation became the primary modality of management patients. This includes anal cancer, locally advanced cervical cancer or larynx cancer, small intracranial metastases, and now is an evolving consideration for low-lying rectal cancers. Whether or not a pCR can be observed in a substantial proportion of breast cancer patients and whether biomarkers could be prognostic of pCR rates remain to be seen. In the meantime, these are certainly provocative concepts awaiting future investigation.

## Conclusions

In summary, PAPBI is an innovative approach to the delivery of radiation therapy as a part of breast conservation for patients with early stage breast cancer. As has been shown more extensively in the post-operative setting, PAPBI appears to be safe and has a number of advantages as compared to APBI currently being practiced across the US. This includes smaller treatment volumes, more accurate image guidance, resection of high-dose treatment area, ability to have pre- and post-RT tissue for response assessment and a possible de-escalation of systemic therapy and reduced surgical volume. While promising, significant work remains to be done in carrying out prospective, randomized, Phase III clinical trials with longitudinal safety and efficacy data comparing PABPI to standard WBRT or post-operative APBI.

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**Table 1**

Summary of ongoing and recently accrued postoperative and postoperative APBI studies

| Institution (TRIAL) | Phase | APBI | Dose | Clinical Trials.gov ID | Notes | Study start date | Primary outcomes |
|---|---|---|---|---|---|---|---|
| Juravinski Cancer Center | Phase I | Pre-operative | 8 Gy ×5 EOD | NCT02065960 | SBRT | February 2014 | Feasibility |
| Georgetown University | Phase I–II | Adjuvant | 6 Gy ×5 | NCT02365714 | CK SBRT | February 2015 | Feasibility |
| Laurentian University Jewish General Hospital | Phase II | Pre-operative | 21 Gy ×1 | NCT02212860 | SBRT | March 2015 | Toxicity |
| Georgetown University (SIGNAL TRIAL) | Multi-institutional registry trial | Adjuvant | 5 fractions | NCT02457117 | CK SBRT | May 2015 | Local failure |
| Duke University | Phase II | Pre-operative | 21 Gy ×1 | NCT02482376 | SBRT | October 2015 | Cosmesis |
| University of Texas Southwestern | Phase I | Adjuvant dose escalation | 22.5–30 Gy ×1 | NCT02685332 | SBRT | March 2016 | Dose tolerance |
| The Netherlands Cancer Institute, Institut Gustave Roussy, Karolinska Institut, University Medical Centre Utrecht (PAPBI Trial) | Phase II | Pre-operative | 4 Gy ×10 or 5 Gy ×6 | NCT01024582 | 3-DCRT, IMRT | April 2010 | Local failure |
| Maisonneuve-Rosemont Hospital (SPORT TRIAL) | Phase I | Pre-operative | 15, 18, or 20 Gy ×1 | NCT01717261 | SBRT | August 2012 | Acute toxicity |
| University Medical Center Utrecht (ABLATIVE TRIAL) | Phase I | Pre-operative → BCS 6 months | 15-20 Gy ×1 | NCT02316561 | Partial breast IMRT | October 2014 | pCR |
| Ohio State University | Phase I, pilot | Pre-operative | 10 fractions BID for 5 days | NCT02186470 | IMRT, prone | June 2015 | Acute toxicity |
| Medical College of Wisconsin | Phase II | Pre-operative | 5 fractions | NCT02728076 | 3-DCRT, MRI guided | May 2016 | Postoperative complications |
| The Netherlands Cancer Institute (PAPBI-2) | Phase III | Pre *vs.* postoperative APBI | 28.5 Gy in 5 fractions | NCT02913729 | Partial breast IMRT | November 2016 | Cosmesis |
| University Hospital, Grenoble (NeoAPBI 01) | Phase II randomized | Chemo *vs.* chemo + postoperative APBI | 25 Gy in 10 BID fractions | NCT02806258 | Partial breast 3-DCRT | March 2016 | pCR |

APBI, accelerated partial breast irradiation; EOD, every other day; SBRT, stereotactic body radiation therapy; CK, CyberKnife; 3-DCRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; BCS, breast-conserving surgery; MRI, magnetic resonance imaging; pCR, pathologic complete response; BID, twice daily.