

Scientific Article

Partial Breast Irradiation and Surgical Clip Usage for Tumor Bed Delineation After Breast-Conserving Surgery in Canada: A Radiation Oncology Perspective



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Abstract

Purpose: Our purpose was to evaluate the usage and perceived benefit of surgical clips for breast radiation therapy planning in Canada, focusing on partial breast irradiation (PBI) after breast-conserving surgery.

Methods and Materials: A retrospective institutional review identified patients eligible for PBI based on clinicopathologic criteria, and tumor bed visualization was determined from computed tomography-planning scans. An online survey was subsequently distributed to Canadian radiation oncologists addressing the usage and added value of surgical clips for breast radiation therapy planning purposes. The survey also evaluated PBI usage and regimens. Responses were collected over a 4-week period. PBI regimen usage at our institution was also reviewed from May 1 to December 18, 2020.

Results: Based on clinicopathologic criteria, 306 patients were identified between 2013 and 2018 who were eligible for PBI. However, only 24% (72/306) of cases were noted to have surgical clips, of which over 50% did not assist in tumor bed localization due to inconsistent clip positioning. Similarly, nearly two-thirds (28/43) of survey respondents indicated that surgical clips are placed in the tumor bed in less than 50% of cases. Almost all respondents (42/43) indicated that surgical clips facilitate breast radiation therapy planning and favor the development of guidelines to increase the consistent placement of surgical clips in the tumor bed after breast-conserving surgery. Approximately two-thirds of respondents (28/43) offer PBI to eligible patients as routine treatment, with moderate hypofractionated regimens most commonly recommended. However, the 1-week daily regimen of 26 Gy in 5 fractions is now offered to the majority (77%) of patients at our institution.

Conclusions: There was strong agreement among Canadian radiation oncologists that surgical clip placement facilitates breast radiation therapy planning, and most favor the development of surgical guidelines for the consistent placement of surgical clips in this setting. With the growing use of PBI, accurate localization of the tumor bed is extremely important.

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Introduction

Clinical trials examining the benefit of whole breast irradiation (WBI) after breast-conserving surgery for early stage breast cancer have consistently shown a decreased risk of recurrent disease with WBI.¹ After breast-conserving surgery, the majority of local recurrences occur near the primary tumor bed.²⁻⁷ Therefore, several randomized clinical trials have investigated partial breast irradiation (PBI), which treats the surgical or tumor bed, as an option to WBI. PBI approaches have included multisource interstitial brachytherapy, balloon-based applicators, intraoperative electrons or low energy photons, and external beam radiation therapy (RT).⁸

The randomized phase 3 clinical trials evaluating PBI with external beam techniques have demonstrated noninferior ipsilateral breast tumor recurrence compared with WBI, with 5 to 10 years of follow-up.⁹⁻¹² The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group 0413 randomized phase 3 equivalence trial evaluated a variety of PBI techniques, and the subgroup of patients receiving external beam PBI was also found to have noninferior ipsilateral breast tumor recurrence compared with WBI.¹³ Although PBI typically minimizes normal tissue toxicity compared with WBI, the Canadian Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) trial¹¹ reported increased late toxicity with the PBI regimen of 38.5 Gy in 10 fractions delivered twice daily over 1 week, predominantly due to increased grade 2 induration or fibrosis.¹¹ Therefore, there are also ongoing prospective phase 2 studies in Canada evaluating other PBI regimens, including 27 Gy in 5 daily fractions (National Institutes of Health Clinical Trials [NCT], NCT02681107)¹⁴ and 30 Gy versus 27.5 Gy in 5 daily fractions (NCT02637024). In contrast, the NSABP B-39/ Radiation Therapy Oncology Group 0413 trial, which evaluated the same PBI regimen as that used in the RAPID trial, reported similar late treatment-related toxicities for WBI and PBI.¹³ More recently, the 5-year results of the United Kingdom (UK), faster radiotherapy for breast cancer patients (FAST)-Forward trial¹⁵ reported noninferior local control and normal tissue toxicity comparing WBI with 26 Gy in 5 fractions to 40 Gy in 15 fractions. The option of 26 Gy in 5 daily fractions has recently been considered for PBI.^{16,17}

The American Society of Radiation Oncology (ASTRO) guidelines recommend PBI for women 50 years or older with invasive ductal carcinoma of 2 cm or less in size, no lymphovascular invasion, no extensive intraductal component, estrogen receptor positive, margins negative by at least 2 mm, node negative, no use of neoadjuvant systemic therapy, or with low-risk ductal carcinoma in situ (DCIS) (screen-detected, unifocal,

nuclear grade 1 or 2, size ≤ 2.5 cm, with margins ≥ 3 mm).¹⁸ Therefore, in carefully selected patients with early stage breast cancer, PBI provides a safe alternative to WBI with limited normal tissue toxicity.

In addition to the selection of suitable patients based on age and clinicopathologic factors, accurate localization of the tumor bed on computed tomography (CT)-planning scans is required for the delivery of external beam PBI and the delivery of boost after WBI, and it also improves the quality of breast RT in general. Several studies have reported on the importance of surgical clips in demarcating the tumor bed,¹⁹⁻²² and an audit of the UK IMPORT LOW trial demonstrated that titanium clips provided the most accurate and reliable method of tumor bed localization.²³ These findings informed the British surgical guidelines for the management of breast cancer with regard to the marking of the surgical bed with clips during breast-conserving surgery to facilitate breast RT.²⁴ The optimal placement and number of surgical clips after breast-conserving surgery have also been described to assist in the delivery of external beam RT for WBI, PBI, or boost.²⁵⁻²⁷ These guidelines and basic principles regarding consistent marking of the tumor bed with clips are becoming increasingly important for breast RT due to the frequent use of oncoplastic procedures in contemporary breast conservation techniques, whereby the tumor bed is typically poorly visualized in the postoperative setting.²⁸ It is estimated that 32% (21,388/67,878) of women diagnosed with breast cancer in England between the years 2012 to 2016 were eligible for PBI²⁹; therefore, clear visualization of the tumor bed after breast-conserving surgery is essential to maximize local therapy options for a sizeable proportion of patients with breast cancer with low-risk disease.

In Canada, there is increasing interest in the use of PBI as part of routine treatment for women with breast cancer who meet the ASTRO suitability criteria.¹⁸ However, surgical clips are not consistently used in breast-conserving surgery, and there are no defined surgical guidelines in Canada in this area. Therefore, we sought to: (1) determine the proportion of women with early breast cancer eligible for PBI at our institution with clear visualization of the tumor bed, (2) conduct a survey aimed to better understand the perceived usage and value of surgical clips, as well as the patterns of PBI practice in Canada, and (3) examine the current PBI practice at our institution.

Methods and Materials

Evaluation of PBI suitability

Institutional research ethics board approval was obtained (18-5897) to retrospectively identify patients

Table 1 CVS of 306 patients with breast cancer eligible for PBI based on clinicopathologic criteria

CVS	Number (%)
1	34 (11)
2	67 (22)
3	92 (30)
4	88 (29)
5	25 (8)

Abbreviations: CVS = cavity visualization scores; PBI = partial breast irradiation.

CVS 1 = no visible cavity, CVS 2 = heterogeneous cavity with indistinct margins, CVS 3 = heterogeneous cavity with some distinct margins, CVS 4 = mildly heterogeneous cavity with mostly distinct margins, and CVS 5 = homogeneous cavity with clearly identified margins.

eligible for PBI from January 1, 2013, to November 1, 2018, who met the ASTRO clinicopathologic criteria and were suitable for PBI radiologically.¹⁸ CT-planning scans of eligible patients were reviewed to assess for the presence of surgical clips and were assigned cavity visualization scores (CVS)³⁰ (CVS range: 1 [cavity not visualized] through 5 [all cavity margins clearly defined and a homogeneous appearance]). These features were used to determine whether cases were considered radiologically suitable for PBI.

Survey

A survey entitled “Use of Surgical Clips and Adjuvant Breast Radiotherapy Treatment Options for Early Breast Cancer” received institutional research ethics board approval (20-5951) and was distributed by email to 256 radiation oncologists in Canada (whose practice includes breast cancer treatment) by the Canadian Association of Radiation Oncology. Anonymized survey responses were collected from January 21 to February 18, 2020. In total, respondents answered 5 questions (Supplementary Materials) that addressed the usage and added value of surgical clips for breast RT planning purposes. The survey also evaluated the different regimens and usage of PBI in Canada. Participation was voluntary, and completion and return of the online survey were taken as proof that participants agreed their responses would be used for this research survey.

Current PBI utilization

The 26 Gy in 5 fraction daily regimen for PBI was adopted at our institution after the publication of the UK FAST-Forward trial,¹⁵ and the number of PBI courses and regimens used from May 1 to December 18, 2020, were determined (institutional waiver 20-0464). For

statistical analyses, the Pearson's χ^2 independence test was performed. All tests were 2-sided, and a *P* value less than .05 was considered statistically significant.

Results

Patients with early breast cancer suitable for PBI

Of 1051 cases identified and deemed eligible for PBI based on age, grade and tumor size, 306 (29%) met all the pathologic criteria. The median age of eligible cases was 65 years (range, 55-88 years). The majority (83%; 254/306) had invasive disease, and 17% (52/306) had DCIS.

CT-planning scans were evaluated for CVS (Table 1) and surgical clips. Overall, 66% (201/306) of cases had both CVS ≥ 3 and surgical clips placed that facilitated localization of the tumor bed. However, 34% (105/306) of cases were unsuitable for PBI radiologically, due to low CVS, lack of surgical clips, or clip placement that did not facilitate tumor bed localization (Fig 1). Indeed, tumor bed clips were noted in 24% of cases (72/306), of which only 47% (34/72) were suitable for PBI.

When surgical clip usage was examined by the year of breast surgery, cases from 2016 to 2018 (48/146) were about twice as likely to have clips compared with those from 2013 to 2015 (24/160, 2-sided Pearson's χ^2 independence test *P* = .0004) (Table 2). However, the use of clips did not increase significantly from 2013 to 2015 (about 15% of cases per year, χ^2 *P* = .8) or from 2016 to 2018 (about one-third of cases per year, χ^2 *P* = .8) (Table 2).

Survey results

Our institutional review revealed low surgical clip use that affected PBI suitability. We proceeded to conduct a national survey addressing the usage of surgical clips in the setting of breast-conserving surgery for early breast cancer. There were 43 completed surveys. The survey results and individual responses are provided in Supplementary Materials. Almost all respondents (97.7%; 42/43) indicated that the delineation of the tumor bed with surgical clips assists in breast RT planning for WBI, PBI, boost, or after oncoplastic breast surgery. However, a substantial proportion of respondents (39.5%; 17/43) indicated that surgical clips are placed in the tumor bed after breast-conserving surgery in less than 25% of cases (Fig 2). Surgical clip placement in the tumor bed was reported at 25.6% (11/43) in 25% to 50% of cases, 14.0% (6/43) in 50% to 75% of cases, and 20.9% (9/43) in more than 75% of cases (Fig 2). Therefore, overall,

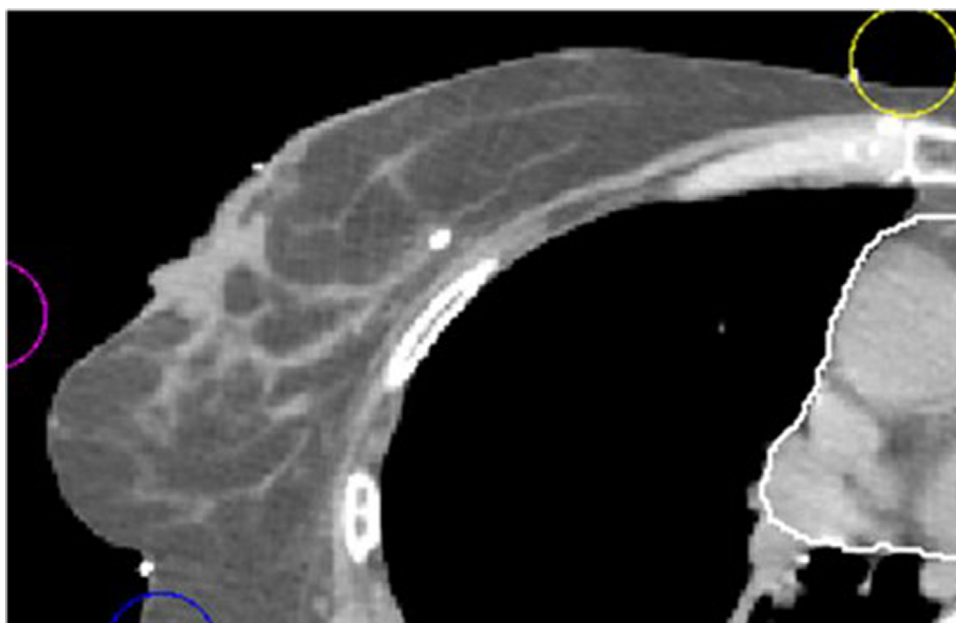


Fig. 1 Computed tomography-planning scan of a representative case demonstrating low cavity visualization scores and surgical clips that do not aid in the localization of the tumor bed.

approximately two-thirds (28/43) of the respondents indicated that surgical clips were placed in the tumor bed in less than 50% of cases after breast-conserving surgery. There was strong support from the respondents (97.7%; 42/43) for the development of guidelines for standard clip placement in the tumor bed for patients undergoing breast-conserving surgery to facilitate RT planning.

With the increasing use of PBI, participants were asked if they offer PBI as part of routine treatment. The majority of respondents (65.1%; 28/43) indicated that they offer PBI to suitable patients with breast cancer (Fig 3A). The most commonly recommended regimen was a moderate hypofractionated PBI regimen of 40 Gy in 15 daily fractions over 3 weeks or an equivalent daily regimen, such as 42.50 Gy in 16 fractions (60.7%; 17/28) (Fig 3B). PBI regimens of either 27 Gy or 27.5 Gy in 5 daily fractions was recommended by 17.9% (5/28), and “other” regimens were recommended by 20.9% (6/28) (Fig 3B). These other PBI regimens included 30 Gy in 5 fractions on alternating days over 2 weeks (3/28) or 38.5 Gy in 10 fractions delivered twice daily over 1 week (3/

28) (Fig 3B). For those respondents who indicated that they do not offer PBI, 73.3% (11/15) would only offer PBI to patients in clinical trial, and the remaining 26.7% (4/15) rarely or never offer PBI whether on trial or not (Fig 3C). The majority of respondents (91%; 39/43) have experience with PBI whether recommended on or off clinical trial.

Of the respondents who would offer PBI as part of routine treatment, 41.1% (7/17) also indicated that surgical clips were placed in the tumor bed in less than 25% of cases (Table E1). Similarly, of the respondents who do not offer PBI off clinical trial, approximately 59% (10/17) also indicated that surgical clips were placed in the

Ranges of surgical clip usage, (%)

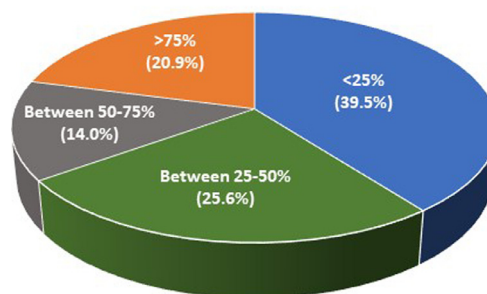


Fig. 2 Ranges of surgical clip use after breast-conserving surgery (<25%, between 25%-50%, between 50%-75%, and >75%) and the responses indicating how often surgical clips are noted (%).

Table 2 Surgical clips by year of breast-conserving surgery

Year	2013	2014	2015	2016	2017	2018
Total cases	53	49	58	44	43	59
Clips n, (%)	7 (13%)	7 (14%)	10 (17%)	16 (36%)	13 (30%)	19 (32%)

The total number of eligible cases per year and the corresponding number and percentage of cases with surgical clips are displayed.

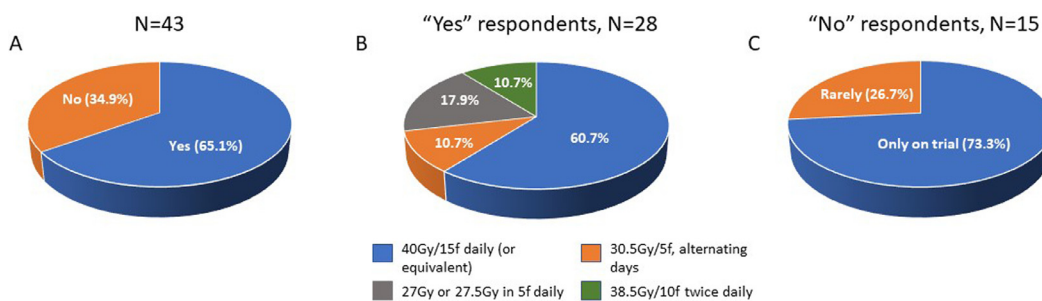


Fig. 3 (A) The proportion of respondents who would (“Yes”) or would not (“No”) offer partial breast irradiation (PBI) as routine treatment for eligible patients. (B) Of the respondents who offer PBI as routine treatment, the different PBI regimens and relative usage are displayed. (C) The respondents who do not offer PBI off clinical trial, the proportion of respondents who only offer PBI on trial (“Only on trial”), and those who rarely offer PBI whether on trial or not (“Rarely”) are shown. *Abbreviation:* F = fraction.

tumor bed in less than 25% of cases (Table E1). Of the 4 respondents who rarely or never offer PBI whether on clinical trial or not, 100% (4/4) also indicated that surgical clips were visualized in less than 25% of cases (Table E1). Therefore, collectively, a substantial proportion of respondents indicated that surgical clips were used in less than 25% of cases, but the proportion was highest in respondents who rarely offer PBI or only offer it in clinical trial.

Current PBI utilization

Since the publication of the FAST-Forward trial in late April 2020,¹⁵ the 26 Gy in 5 fraction regimen has been increasingly used at our center for the delivery of PBI. From May 1 to December 18, 2020, a total of 39 PBI courses were delivered, with 77% (30/39) using the 26 Gy in 5 fraction regimen (Table 3); from November 12 to December 18, 2020, 100% (14/14) of PBI cases were delivered with this 5-fraction regimen.

Discussion

Our institutional experience identified low usage of surgical clips in the delineation of the tumor bed in the setting of breast-conserving surgery for women with low-risk breast cancer. Although this review was limited by its retrospective nature and subjective categorization of tumor bed visibility, it does illustrate that a proportion of

otherwise eligible patients may be unsuitable for PBI due to poor visualization of the tumor bed and lack of surgical clips. Although clip usage increased 2-fold comparing the periods of 2013 to 2015 and 2016 to 2018, clips were still only used in about one-third of cases each year from 2016 to 2018. This issue was explored further by a national survey.

The survey results demonstrate that most Canadian radiation oncologist respondents consider PBI as an alternative to WBI for eligible patients with early breast cancer. However, there is infrequent use of surgical clips after breast-conserving surgery, which may limit the ability to deliver PBI. With the increasing use of surgical techniques that minimize clear visualization of the tumor bed, the consistent placement of surgical clips is becoming even more important for breast RT, particularly for PBI and boost. To address this issue, specific recommendations have included the consistent placement of 4 to 6 clips in the walls of the surgical cavity at the level where the primary tumor was located representing the boundaries of the resection; insertion of clips before repositioning or rotation of breast tissue during oncoplastic procedures; detailed operative reports that include the number of clips used, clip placement, and closure technique; and close multidisciplinary collaboration between surgeons and radiation oncologists to augment reliable and accurate localization of the tumor bed for breast RT planning.^{23,27,28}

Subsequent to the development of surgical guidelines in the UK for clip usage after breast-conserving surgery,²⁴ variability in compliance was noted, with a higher proportional use of clips at centers involved in breast RT randomized clinical trials.³¹ For example, after joining a clinical trial, the number of centers routinely using tumor bed clips to facilitate breast RT planning increased from 5 (19%) to 21 (81%).³² Based on these results, the authors suggested that clip insertion should be audited and considered as a measure of quality in breast surgery.³¹ Such quality control is not unreasonable as clips likely add to better local control based on improved localization of the tumor bed. Furthermore, there are no real barriers to clip

Table 3 PBI utilization from May 1 to December 18, 2020, and regimen

PBI regimen	26 Gy/5f	40 Gy/15f	Other
Courses, n (%)	30 (77%)	7 (18%)	2 (5%)

Abbreviations: f = fraction; PBI = partial breast irradiation. There were 39 PBI courses during this period. Other – 28.5 Gy/5f once weekly (1) and 45 Gy/25 f daily (1).

usage based on cost, and clip insertion does not substantially increase operative time.³³

The majority of respondents from this survey indicated that they recommend PBI using a moderate hypofractionated regimen over 3 weeks. However, it is not clear whether respondents would now consider offering PBI using 26 Gy in 5 daily fractions based on the 5-year results of the FAST-Forward trial¹⁵; this 1-week regimen is now offered to the majority of PBI eligible patients with breast cancer at our institution.

One of the main limitations of this survey was the relatively small proportion of respondents, and it is possible that an extended period of response would have increased participation. The survey was also sent to any radiation oncologist whose practice includes breast cancer treatment, regardless of whether it is a primary, secondary, or tertiary focus of their practice; therefore, it is possible that radiation oncologists with a primary focus in breast cancer treatment would have been more inclined to complete the survey. However, there was strong agreement among respondents of the added value of surgical clips for breast RT planning and the need for surgical guidelines to support greater awareness of the benefits of clips in the accurate and reliable delineation of the tumor bed. Furthermore, we did not collect information that would identify specific cancer centers or data that would indicate regional or provincial variation across the country in terms of surgical clip usage, the recommendation of PBI, or regimen type. However certain regimens, such as the 27 Gy in 5 daily fractions regimen, were likely recommended by respondents in Alberta, where this regimen is currently being evaluated in a prospective clinical trial. Lastly, the option of 26 Gy in 5 daily fractions has recently been considered for PBI due to the coronavirus disease 2019 pandemic as a risk mitigation strategy^{16,17} and may be adopted postpandemic in Canada.

In conclusion, for carefully selected women with early stage breast cancer, PBI is increasingly offered in Canada as an option for local treatment after breast-conserving surgery. However, the ability to deliver PBI depends on the accurate localization of the tumor bed on CT-planning scans, which in turn is required for optimal local control. Guidelines for the placement of surgical clips in the tumor bed cavity at the time of breast-conserving surgery have facilitated breast RT planning in other countries, although it is clear that ongoing collaboration between surgeons and radiation oncologists is important to ensure consistent implementation of such guidelines.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.adro.2021.100701](https://doi.org/10.1016/j.adro.2021.100701).

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