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Impact of the Delineation Accuracy of Lumpectomy Cavity on Planning Target Volume in Partial-Breast Irradiation Using Brachytherapy and External-Beam Radiotherapy

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ABSTRACT

Background: In partial-breast irradiation (PBI), an accurate target volume delineation based on the lumpectomy cavity (LC) has been reported to remain difficult due to uncertain LC identification. However, the impact of accurate LC delineation on the planning target volume (PTV) has not been investigated.

Material and methods: Between September 2018 and April 2020, 159 patients receiving perioperative PBI with multicather-interstitial brachytherapy were evaluated. While LC delineation using implanted catheters as fiducial markers was used as a reference, conventional LC was virtually delineated on computed tomography with clips. $PTV_{1\text{-cm margin}}$ and $PTV_{2\text{-cm margin}}$, which means 1cm and 2cm expansion from LC, were developed and assumed for brachytherapy and external-beam PBI, respectively. The target accuracy and the impact of the delineation accuracy of LC on PTVs were evaluated. The geographic miss index (GMI) and normal tissue index (NTI) were used as accuracy indices and were defined as the percentage of under- and overestimating volume, respectively.

Results: The $PTV_{1\text{-cm margin}}$ and $PTV_{2\text{-cm margin}}$ were significantly larger than the reference volume, $57.9cm^3$ vs. $37.9cm^3$ ($P<0.001$) and $113.2cm^3$ vs. $93.8cm^3$ ($P<0.001$), respectively. The GMI and NTI of LC were 27.3% and 41.2%, respectively. Although the GMI in the $PTV_{1\text{-cm margin}}$ and $PTV_{2\text{-cm margin}}$ was significantly reduced to 9.8% ($P<0.0001$) and 9.9% ($P<0.0001$), respectively, the NTI was not significantly improved in the $PTV_{1\text{-cm margin}}$, which was 41.8% ($P=0.60$) but was improved in $PTV_{2\text{-cm margin}}$, which was 23.1% ($P<0.0001$).

Conclusion: The GMI in $PTV_{1\text{-cm margin}}$ was reduced to be as low as $PTV_{2\text{-cm margin}}$. Although $PTV_{2\text{-cm margin}}$ was associated with lower NTI, the absolute volume was almost double with $PTV_{1\text{-cm margin}}$. Although further research is required, brachytherapy-based PBI may be a reasonable option to achieve tumor control and cosmesis using the conventional delineation method.

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INTRODUCTION

Breast-conserving therapy (BCT) consisting of lumpectomy and whole-breast irradiation (WBI) has been the standard treatment for early-stage breast cancer.[1,2] However, the adjuvant radiotherapy with a small fraction size to the entire breast needs 3 to 5 weeks of daily visit to the radiation facility and an unnecessary radiation exposure to the surrounding normal tissues. Partial-breast irradiation (PBI) has been introduced as an alternative radiotherapy option for more conveniences and less toxicities. Various techniques of PBI have been introduced including brachytherapy with multicatheter or single-entry device, external-beam radiotherapy (EBRT) with three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy, and intraoperative radiotherapy (IORT) with low-kilovolt X-ray or electron.[3,4,5,6,7,8,9,10]

The concept of PBI in BCT was the delivery of the large fraction size of radiotherapy to the limited breast tissue to eradicate microscopic residual disease after lumpectomy. The clinical target volume (CTV) is defined as the adjacent breast glandular tissue from the lumpectomy cavity (LC) with 1–2cm margins depending on the surgical-free margins.[11,12] The planning target volume (PTV) has been reported to vary with PBI technique. While PTV in brachytherapy-based PBI and IORT technique has been generally found to equal to CTV, the PBI using EBRT needs an additional expansion from the CTV, which compensates for patients' movement and set-up error.[11,12] Regardless of the PBI technique, the accurate target delineation is crucial, because under-delineating target volume to at-risk tissues that are not treated and over-delineating target volume without necessarily being treated by a higher dose might cause added risks of ipsilateral tumor recurrence (IBTR) and worse cosmesis, respectively.

Among various PBI techniques, meta-analyses from recent randomized clinical trials have shown that multicatheter interstitial brachytherapy (MIB) and EBRT provide similar outcomes in tumor control and toxicities to WBI after lumpectomy[13,14,15], in which the target volume is delineated using the LC based on the computed tomography (CT) with the four or more clips' assistance. However, the issue of the accurate LC delineation has remained, because of the difficult identification of the LC boundary on CT and the possible migration of the limited number of fiducial markers.[16] In our institution, perioperative MIB-PBI has been performed using the intraoperative catheter implant, of which the LC on catheter-based delineation has been reported as accurately as possible because of the usage of the implanted catheters as fiducial markers.[17,18]

In this study, the LC was delineated on CT with clips as a conventional method compared with that on catheter-based delineation as a reference. The different PTV definitions assumed to perform brachytherapy-based PBI and EBRT-PBI have been developed to evaluate the target accuracy, and the impact of the delineating accuracy of the LC on the PTVs has also been assessed.

MATERIAL AND METHODS

Patient and image characteristics

Between September 2018 and April 2020, patients who had received perioperative MIB-PBI after lumpectomy were evaluated. The eligibility criteria included age of 40 years or older, tumor diameter of 3 cm or less, negative sentinel node for metastasis, and clear margins on specimen mammography. Patient characteristics including body mass index (BMI) and excised tissue weights were obtained from an electric medical record. All patients underwent preoperative contrast-enhanced CT for a simulation and non-contrast-enhanced CT immediately after surgery with the ipsilateral arm abducted for PBI planning. During contouring target volumes, a radiation technician assigned the cavity visualization score (CVS) of 1–5 as follows: CVS-1, cavity not visualized; CVS-2, cavity visualized but margins indistinct; CVS-3, cavity visualized with some distinct margins and heterogeneous appearance on CT; CVS-4, cavity with mild heterogeneity on CT and the majority of margins distinct; and CVS-5, homogenous appearance of the cavity on CT and all margins clearly seen.[19] The total breast volumes have been calculated using CT with anatomical boundaries according to the RTOG Breast Cancer Atlas.[20] Postoperative CT features including the CVS scores, the distances between the skin and the chest-wall, the cavity volumes on the cavity-based delineation, and the breast volume were also included for analysis.

Technique of lumpectomy and perioperative MIB-PBI

The details of the perioperative MIB-PBI technique had been reported previously.[21,22] Generally, lumpectomy was performed with 1cm gross surgical margin. The excised tissue was sent for specimen mammography to confirm free margin. In the surgical cavity, the edge of the depth was approximated, and four clips were placed at the upper, lower, medial, and lateral cavity wall. After confirming negative margins and sentinel nodes for metastasis, the rigid steel needles were inserted with reference to preoperative radiation planning, and they were replaced by plastic catheters for introducing iridium 192. Normal saline was injected after closing the wound to keep the breast contour during radiotherapy. Treatment was initiated on the same day of the surgery. According to the recommended schedule of the European society for radiation and oncology-advisory committee on radiation oncology practice (ESTRO-ACROP) guideline[23], the prescribed dose was 32Gy in 8 twice daily fractions of 4Gy delivered using a high-dose rate remote after-loading equipment.

Catheter-based delineation on MIB-PBI and virtual delineation on conventional method

During surgery for MIB-PBI, the distances between upper and lower edges of the glandular tissue and needles and from the point of the bottom of each catheter to the cavity walls were measured using the catheter-based delineation technique, which was put into the CT image as an additional piece of information to the CT image with clips.[17] As a conventional delineating technique for this study, one radiation oncologist (N.N.) and one radiation technician (T.S.) blindly delineated the LC as a re-planning with an agreement based on the visible seroma with clips identification.

Based on the contoured cavity using two different delineation techniques, CTV was defined as 1cm compassing LC. PTV was developed on two different definitions for different PBI techniques; no CTV-PTV margin was observed, meaning 1cm expansion from the LC was assumed for brachytherapy-based PBI: $PTV_{1\text{-cm margin}}$ and an additional 1cm CT-PTV margin, meaning 2cm expansion from the LC was assumed for EBRT-PBI: $PTV_{2\text{-cm margin}}$.

Evaluation of delineation accuracy of target volume on conventional method

The target volume on catheter-based delineation was defined as the radiological field (RF), which was considered to be a real delineating volume and was used as a reference. The virtually delineating target volume on CT with clips was defined as the clinical field (CF) for a comparison. The overlapped volume between RF and CF was defined as the shared field (SF). Figure 1 shows the flowchart of the study design. The target delineation accuracy was investigated using the following accuracy indices: the geographic miss index (GMI) to identify underestimation and the unintended normal tissue index (NTI) to identify overestimation.[24] The GMI was defined as the ratio of the under-outlining volume with the conventionally contoured volume to the reference volume, (RF − SF)/RF x 100%, and the NTI as the ratio of the over-outlining volume with the conventionally countered volume to the conventionally delineated volume, (CF − SF)/CF x 100% (Figure 2). The GMI represented the high-risk volume of local recurrence within the reference volume, which was not included in the conventionally delineated volume. The NTI measured the percentage of the conventionally delineated volume out of the reference volume, which received unnecessary radiotherapy. Therefore, the GMI and the NTI should be as low as possible. This study was approved by the ethics committee of the Tokushukai medical group.

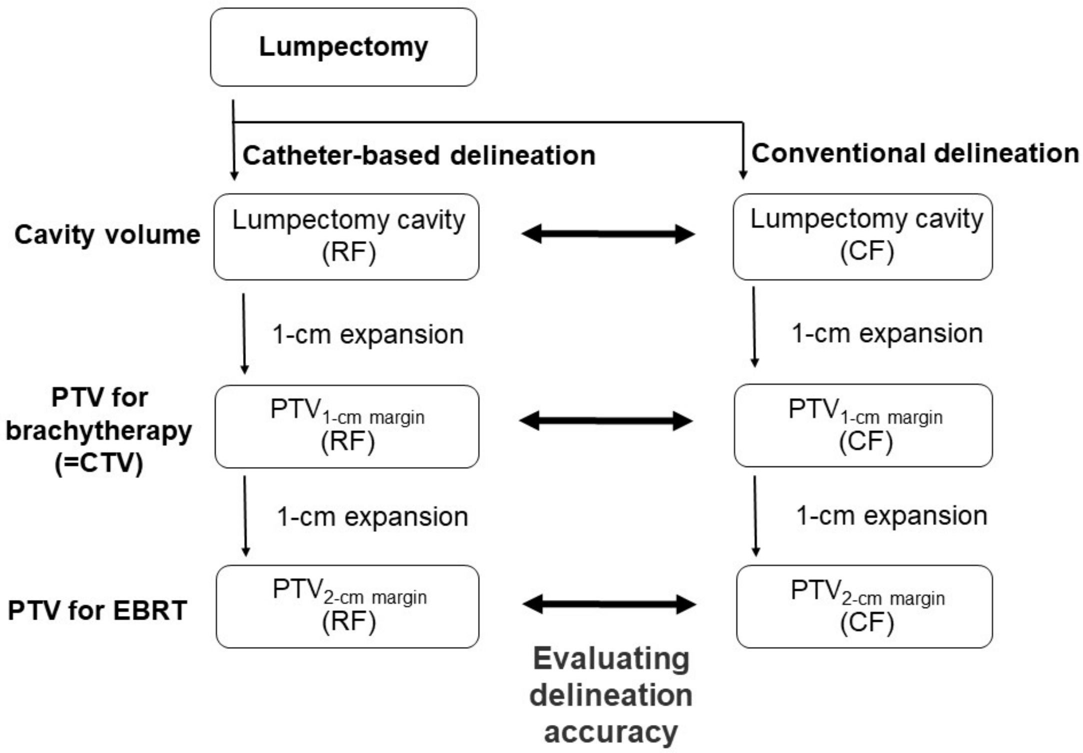

Figure 1. Flowchart of the study design.

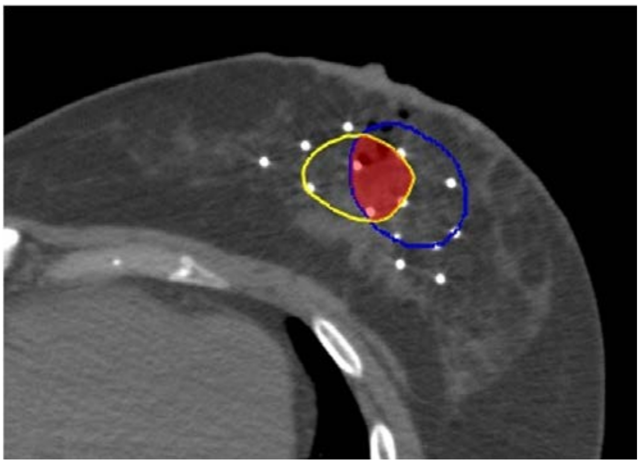

Figure 2. Definition of the geographic miss index and the normal tissue index. The lumpectomy cavity on the catheter-based delineation (yellow) indicates the radiological field (RF) as a reference volume. The conventionally delineated lumpectomy cavity (blue) indicates the clinical field (CF) for a comparison. The overlapped volume (red) indicates the shared field (SF). The geographic miss index (GMI) and normal tissue index (NTI) have been calculated according to the following formula: GMI = (RF − SF)/RF x 100% and NTI = (CF − SF)/CF x 100%

Statistics

Quantitative data following a normal distribution were expressed as mean with standard deviation (SD) and were analyzed using t-test and ANOVA for normally distributed data. All correlations were calculated by linear regression analysis and calculation of β-coefficients at 95% confidence intervals. A P-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 27.0 (Statistical Package for Social Sciences) software (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient and image characteristics and target volumes using the two delineation methods

A total of 159 patients received MIB-PBI, of whom all imaging data were available for this study. Table 1 shows the patient and image characteristics and target volumes using the two delineation methods. The mean age ± SD was 58.0 ± 11.5 years old, of whom the BMI was 22.8 ± 3.9 kg/m^2. The distribution of CVS was as follows: CVS-1, 12 (7.6%); CVS-2, 34 (21.4%); CVS-3, 43 (27.0%); CVS-4, 48 (30.2%); and CVS-5, 22 (13.8%). The mean ± SD of the absolute volume of LC, $PTV_{1\text{-cm margin}}$, and $PTV_{2\text{-cm margin}}$ on the catheter-based delineation was 11.3 ± 6.3cm^3, 37.9 ± 19.3cm^3, and 93.8 ± 42.1cm^3, respectively. The mean ± SD of relative volume to the entire breast in LC, $PTV_{1\text{-cm margin}}$, and $PTV_{2\text{-cm margin}}$ was 3.4% ± 2.0%, 10.5% ± 4.0%, and 26.4% ± 8.0%, respectively. In the conventional delineation, the absolute target volumes of the LC, $PTV_{1\text{-cm margin}}$, and $PTV_{2\text{-cm margin}}$ were significantly greater than the reference volume, 14.4 ± 8.5cm^3 (P<0.0001), 57.9 ± 26.4cm^3 (P<0.001), and 113.2 ± 52.1cm^3 (P<0.001), respectively. The relative target volumes to the entire breast of the LC, $PTV_{1\text{-cm margin}}$, and $PTV_{2\text{-cm margin}}$ were also significantly larger, 4.4% ± 2.9% (P<0.0001), 17.0% ± 6.8% (P<0.001), and 31.9% ± 9.7% (P<0.001), respectively.

Table 1. Patient and image characteristics and target volumes using two delineation methods (n = 159)

Variables		Mean ± SD (95% CI)	
Age, years		58.7 ± 11.5 (56.9–60.5)	
Body mass index, kg/m^2		22.8 ± 3.9 (22.2–23.4)	
Excised tissue weight, g		22.2 ± 12.6 (20.2–24.1)	
Breast volume, cm^3		393.9 ± 226.5 (358.4–429.3)	
Skin/chest-wall distance, mm		37.0 ± 13.9 (34.8–39.2)	
Cavity visualization score, n (%)			
CVS-1		12 (7.6)	
CVS-2		34 (21.4)	
CVS-3		43 (27.0)	
CVS-4		48 (30.2)	
CVS-5		22 (13.8)	
Delineation target	Reference volume (mean ± SD)	Conventionally delineated volume (mean ± SD)	P-value
Lumpectomy cavity, cm^3	11.3 ± 6.3 (10.3–12.3)	14.4 ± 8.5 (13.1–15.7)	<0.0001
Relative volume, %	3.4 ± 2.0 (3.1–3.7)	4.4 ± 2.9 (4.0–4.9)	<0.0001
$PTV_{1\text{-cm margin}}$, cm^3	37.9 ± 19.3 (34.9–40.5)	57.9 ± 26.4 (53.8–62.1)	<0.0001
Relative volume, %	10.5 ± 4.0 (9.9–11.1)	17.0 ± 6.8 (15.9–18.1)	<0.0001
$PTV_{2\text{-cm margin}}$, cm^3	93.8 ± 42.1 (87.3–100.4)	113.2 ± 52.1(105.0–121.5)	<0.0001
Relative volume, %	26.4 ± 8.0 (25.1–27.6)	31.9 ± 9.7 (30.4–33.4)	<0.0001

SD: standard deviations; CI: confidence interval; CVS: cavity visualization score; PTV: planning target volume

Accuracy index scores of the target volumes and impact of the accuracy of LC on PTV

The mean accuracy index scores ± SD of the GMI and NTI in LC were 27.3% ± 21.3% and 41.2% ± 19.3%, respectively. Among the three categories, a significant improvement in both of the accuracy index scores was observed (P<0.0001). In PTV, the accuracy indexes of the $PTV_{1\text{-cm margin}}$ and $PTV_{2\text{-cm margin}}$ were GMI (9.8% ± 11.8% and 9.9% ± 8.7%) and NTI (41.8% ± 16.0% and 23.1% ± 11.7%), respectively. In the pairwise comparison between the LC and PTV, the GMI in the LC was significantly improved in $PTV_{1\text{-cm margin}}$ (P<0.0001) and $PTV_{2\text{-cm margin}}$ (P<0.0001). The NTI in the LC was not improved in $PTV_{1\text{-cm margin}}$ (P= 0.60) but was improved in PTV2-cm margin (P<0.0001).

Clinical and imaging features affecting the accuracy indexes of LC

Using multivariable analyses with age, BMI, excised tissue weight, breast volume, skin/chest-wall distance, referenced LC volume, and CVS, only the CVS was found to be independently associated with both of the GMI (β=−0.301, P<0.001) and NTI (β=−0.418, P<0.0001) in the LC. Additionally, the distance between the skin/chest-wall and the referred LC was significantly associated with the GMI (β=−0.393, P<0.05) and NTI (β=−0.404, P<0.0001), respectively (Table 2).

Table 2. Association of postoperative imaging variables and GMI and NTI of cavity delineation

Clinical feature	GMI		NTI	
	β-coefficients (95% CI)	P-value	β-coefficients (95% CI)	P-value
Age	0.001 (−0.003–0.003)	0.99	0.049 (−0.001–0.003)	0.48
Body mass index	0.027 (−0.012–0.015)	0.83	0.157 (−0.003–0.019)	0.17
Excised tissue weight	−0.178 (−0.007–0.001)	0.12	0.193 (0.000–0.006)	0.06
Breast volume	−0.110 (0.000–0.000)	0.49	−0.086 (0.000–0.000)	0.54
Skin/chest-wall distance	0.393 (0.001–0.011)	<0.05	0.028 (−0.003–0.004)	0.83
*Lumpectomy cavity	0.058 (−0.004–0.008)	0.54	−0.404 (−0.017–−0.007)	<0.0001
CVS	−0.301 (−0.087–−0.024)	<0.001	−0.418 (−0.095–−0.045)	<0.0001

Bold indicates statistically significant differences. *Assessed using catheter-based cavity delineation technique as a reference volume. GMI: geographical miss index; NTI: normal tissue index; CI: confidence interval; CVS: cavity visualization score

Association of clinical and imaging features with the influence of LC accuracy to PTV

In a multivariate analysis of the clinical and imaging features including conventionally delineated volume of LC, skin/chest-wall distance, breast volume, and the GMI and NTI of the LC, only the GMI of the LC was found to significantly affect the GMI in the $PTV_{1\text{-cm margin}}$ (β=0.729, P<0.0001) and $PTV_{2\text{-cm margin}}$ (β=0.574, P<0.0001). In the NTI of the PTV, the NTI of the LC was found to significantly affect both of the $PTV_{1\text{-cm margin}}$ (β=0.604, P<0.0001) and $PTV_{2\text{-cm margin}}$ (β=0.603, P<0.0001). While the other factor did not affect the GMI in both PTVs, the conventionally delineated LC (β=0.185, P<0.005 and β=0.272, P<0.0001) and the skin/chest-wall distance (β=−0.532, P<0.0001 and β=−0.338, P<0.005) were also found to be significantly associated with the NTI in $PTV_{1\text{-cm margin}}$ and $PTV_{2\text{-cm margin}}$, respectively (Table 3)

Table 3. Factors affecting accuracy index scores of $PTV_{1\text{-cm margin}}$ and $PTV_{1\text{-cm margin}}$

Variables	$PTV_{1\text{-cm margin}}$		$PTV_{2\text{-cm margin}}$	
	β-coefficients (95% CI)	P-value	β-coefficients (95% CI)	P-value
	GMI			
*Contoured cavity volume	−0.059 (−0.002–−0.001)	0.33	−0.141 (−0.003–−0.000)	0.07
Skin/chest-wall distance	0.132 (0.000–0.003)	0.16	0.111 (0.000–0.003)	0.21
Breast volume	0.061 (0.000–0.000)	0.51	0.022 (0.000–0.000)	0.85
GMI of lumpectomy cavity	0.729 (0.341–0.470)	<0.0001	0.574 (0.174–0.294)	<0.0001
	NTI			
*Contoured cavity volume	0.185 (0.001–0.006)	<0.005	0.272 (0.002–0.005)	<0.0001
Skin/chest-wall distance	−0.532 (−0.008–−0.004)	<0.0001	−0.338 (−0.005–−0.001)	<0.005
Breast volume	0.196 (0.000–0.000)	0.07	0.201 (0.000–0.000)	0.08
NTI of lumpectomy cavity	0.604 (0.409–0.592)	<0.0001	0.603 (0.298–0.438)	<0.0001

Bold indicates statistically significant differences. *Assessed using conventional cavity delineation technique.
PTV: planning target volume; CI: confidence interval; GMI: geographic miss index; NTI: normal tissue index

DISCUSSION

Although the accuracy index of the LC was still moderately high (GMI: 27.3% and NTI: 41.2%) on the modern delineation method using CT with clips, the GMI in $PTV_{1\text{-cm margin}}$ and $PTV_{2\text{-cm margin}}$ was significantly reduced to 9.8% (P<0.0001) and 9.9% (P<0.0001), respectively. The NTI was not significantly improved in the $PTV_{1\text{-cm margin}}$, which was 41.8% (P=0.60), but was improved in $PTV_{2\text{-cm margin}}$, which stood at 23.1% (P<0.0001). However, the absolute volume and the ratio to the entire breast of $PTV_{2\text{-cm margin}}$ (113.2cm^3 and 31.9%) were almost double of the $PTV_{1\text{-cm margin}}$ (57.9cm^3 and 17.0%), respectively.

Recently, PBI in BCT has been investigated as a less invasive and more convenient radiotherapy to WBI since the 1990s. Due to poor delineation of the target volume in addition to less advanced preoperative imaging and systemic therapy, high IBTR has been a concern.[25,26] Also, in the 2000s, meta-analyses of recent clinical trials showed clinically equivalent tumor control by MIB- and EBRT-PBI based on modern 3D image-guided target delineation with WBI.[13,14,15] However, the cosmetic outcomes due to late fibrosis have been observedin some EBRT-PBI techniques.[14,15] Although the causes of a worse cosmesis have been speculated including adjuvant chemotherapy and radiation schedule,[27,28] a larger irradiate volume may cause worse cosmesis due to greater radiation fibrosis formation in the breast.[29,30] Although a smaller target volume was crucial to achieving better cosmesis, an uncertain target delineation on unclear LC tended to be delineated larger than on clear demarcation to avoid the geographic miss.[17,31] Therefore, an accurate target delineation is crucial to achieving not only tumor control but also potential improvement of cosmetic outcomes in PBI.

A number of studies have addressed the issues and evaluated the accuracy of electron boost planning using both indexes. In the 1990s, the patient's surgical records, the surgical scar, and mammographic findings have been used to locate the tumor bed, with the cavity delineation being based on 2D radiographs for a tumor bed boost using electron.[32,33] Since this was a very poor clinical marker for tumor location, the improvement of the accuracy index by multiple clip implants was examined where the GMI and NTI in $PTV_{1\text{-cm margin}}$, $PTV_{2\text{-cm margin}}$, and $PTV_{3\text{-cm margin}}$ were 32.9%, 26.1%, and 18.6% and 14.6%, 13.0%, and 9.7%, respectively.[24] In the early 2000s, LC delineation was routinely made on CT. Although no improvement could be reported on CT only[31], the clips may be helpful in the planning, and CT with multiple clips has been reported to improve the accuracy of $PTV_{3\text{-cm margin}}$ with a GMI of 37% and an NTI of 9%.[34] However, no further reports were found because of the absence of established LC delineation, and the delineation of the target volume on CT with clip has been the golden standard.[12]

In this study, using a catheter-based delineation technique, the GMI of $PTV_{1\text{-cm margin}}$ and $PTV_{2\text{-cm margin}}$ on CT with clips as a conventional method was only 9.8% and 9.9%, respectively. Especially, brachytherapy-based PBI may cover this small geometric miss due to a low-gradient radiotherapy.[35] Conversely, the NTI was still large with 41.8% and 23.1%, respectively. Both accuracy indexes were related to the LC accuracy. Among various clinical features, the clear identification of the LC had the most influence on the accuracy of PTVs[16,17,18,36], but 66% of the patients had three or more CVS in this population. There are several methods to minimize uncertainties reported including the reference of preoperative CT, magnetic resonance imaging-based delineation, clip insertion, and tissue marker insertion.[16,37] However, no method has been established so far to achieve accurate cavity delineation.

CONCLUSION

Studies focusing on the influence of accurate LC delineation to the radiation target for PBI are limited. Regardless of a retrospective analysis based on the hypothetically delineated LC, this study was unique because the cavity using catheter-based delineation technique was supposed to be the true cavity. While $PTV_{1\text{-cm margin}}$ could significantly be reduced as well as $PTV_{2\text{-cm margin}}$, the NTI of the LC was not significantly improved in $PTV_{1\text{-cm}}$ and $PTV_{2\text{-cm margin}}$. Although larger PTV had lower NTI achieving more accurate planning, the absolute target volume and the ratio to the entire breast on conventional delineating technique were almost double compared to those on the catheter-based delineation, with potential implications for cosmesis, which might explain why the results of MIB-PBI were better compared with EBRT-PBI.[38] Therefore, the MIB-PBI based on conventional delineation method could be a reasonable PBI technique to obtain tumor control maintaining satisfactory cosmesis. However, this study had some limitations: First, it is not certain the cavity on catheter-based delineation represented the true one, and the cavity on the conventional method could be affected by the implanted catheters. Second, the target population of the study had relatively small breasts. The PTV expansion is more limited by the organs at risk than in patients with larger breasts.[39] Finally, the most modern EBRT technique may reduce the PTV margin. Further clinical research is required.

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ABBREVIATIONS

BCT: Breast-conserving therapy; WBI: Whole-breast irradiation; PBI: Partial-breast irradiation; EBRT: External-beam radiotherapy; 3D-CRT: 3-dimrnsional conformal radiotherapy ; IMRT: Intensity modulated radiation therapy; IORT: Intraoperative radiotherapy; CTV: Clinical target volume; LC: Lumpectomy cavity; PTV: Planning target volume; MIB: Multicatheter-interstitial brachytherapy; IBTR: Ipsilateral breast tumor recurrence; CT: Computed tomography; GMI: Geographic miss index; NTI: Normal tissue index; BMI: Body mass index; CVS: Cavity visualization score; RF: Radiological field; CF: Clinical field; SF: Shared field; SD: Standard deviation; CI: Confidence interval.

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None.

ETHICAL CONSIDERATIONS

This study was approved by the ethics committee of the Tokushukai medical group, clinical trial registration number: UMIN 000029907

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