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A comparison study between gross tumor volumes defined by preoperative magnetic resonance imaging, postoperative specimens, and tumor bed for radiotherapy after breast-conserving surgery

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Abstract

Background: The identification and contouring of target volume is important for breast-conserving therapy. The aim of the study was to compare preoperative magnetic resonance imaging (MRI), postoperative pathology, excised specimens' (ES) size, and tumor bed (TB) delineation as methods for determining the gross tumor volume (GTV) for radiotherapy after breast-conserving surgery (BCS).

Methods: Thirty-three patients with breast cancer who underwent preoperative MRI and radiotherapy after BCS were enrolled. The GTVs determined by MRI, pathology, and the ES were defined as GTV_{MRI}, GTV_{PAT}, and GTV_{ES}, respectively. GTV_{MRI+1} was defined as a 1.0-cm margin around the GTV_{MRI}. The radiation oncologist delineated GTV of the TB (GTV_{TB}) using planning computed tomography according to ≥5 surgical clips placed in the lumpectomy cavity (LC).

Results: The median GTV_{MRI}, GTV_{MRI+1}, GTV_{PAT}, GTV_{ES}, and GTV_{TB} were 0.97 cm^3 (range, 0.01–6.88), 12.58 cm^3 (range, 3.90–34.13), 0.97 cm^3 (range, 0.01–6.36), 15.46 cm^3 (range, 1.15–70.69), and 19.24 cm^3 (range, 4.72–54.33), respectively. There were no significant differences between GTV_{MRI} and GTV_{PAT}, GTV_{MRI+1} and GTV_{ES}, GTV_{ES} and GTV_{TB} (P=0.188, 0.070, and 0.264, respectively). GTV_{MRI} is positively related with GTV_{PAT}. However, neither GTV_{ES} nor GTV_{TB} correlated with GTV_{MRI} (P=0.071 and 0.378, respectively). Furthermore, neither GTV_{ES} nor GTV_{TB} correlated with GTV_{MRI+1} (P=0.068 and 0.375, respectively).

Conclusion: When ≥5 surgical clips were placed in the LC for BCS, the volume of TB was consistent with the volume of ES. Neither the volume of TB nor the volume of ES correlated significantly with the volume of tumor defined by preoperative MRI.

Abbreviations: APBI = accelerated partial breast irradiation, BCS = breast-conserving surgery, EB-PBI = external-beam partial breast irradiation, ES = excised specimens, GTV = gross tumor volume, LC = lumpectomy cavity, MRI = magnetic resonance imaging, TB = tumor bed.

Keywords: breast-conserving surgery, excised specimen, preoperative magnetic resonance imaging, radiotherapy, tumor bed

Editor: Feng Yang.

AZ and WW have contributed equally to the article.

Funding/support: The study was funded by Medicine and Health Science Technology Development Program of Shandong Province (no. 2013WS0346), Science and Technology Program of Shandong Academy of Medical Sciences (no. 2015-62), and The National Key Research Program of China (no. 2016YFC0904700).

Ethics approval and consent to participate: We are compliant with ethical standards. The patients enrolled have given their consent to participate in our study.

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:2(e5839)

Received: 5 October 2016 / Received in final form: 1 December 2016 / Accepted: 15 December 2016

http://dx.doi.org/10.1097/MD.0000000000005839

1. Introduction

Breast-conserving therapy is the standard treatment in patients with early-stage breast cancer.[1] A meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group revealed that radiotherapy after breast-conserving surgery (BCS) halved the local recurrence rate and reduced the mortality rate.[2] During breast radiotherapy, boost irradiation to the tumor bed (TB) can reduce ipsilateral breast tumor recurrences, especially in young patients or those with a high risk of recurrence.[3,4] Therefore, the identification and contouring of the TB based on surgical clips and/or the seroma is important for boost irradiation.

Because most ipsilateral breast cancer recurrences occur in or nearby the TB, accelerated partial breast irradiation (APBI) has gained popularity in patients with low local recurrence risk.[5,6] External-beam partial breast irradiation (EB-PBI) is one such approach, and the clinical impact of accurate TB delineation according to the boundary of lumpectomy cavity (LC) is paramount when using EB-PBI.[7,8] For a selected group of early-stage breast cancer patients, Polgár et al[9] found ipsilateral breast tumor recurrence rates among patients treated by EB-PBI to be similar to those treated with whole breast irradiation. However, a recent study demonstrated that EB-PBI increased the rates of adverse cosmesis and late-radiation toxicity compared with standard whole breast irradiation.[10] Therefore, the procedures for defining and delineating TB volume should be reviewed.

Compared to conventional imaging modalities such as mammography and ultrasonography, magnetic resonance imaging (MRI) has superior sensitivity and accuracy for the detection and visualization of tumor extent.[11–14] Furthermore, because of high spatial resolution, preoperative MRI can detect occult tumors and provide additional information about the original tumor location.[15–17] However, whether surgeons and radiation oncologists perform surgery or determine irradiation target volume based on preoperative MRI-derived parameters has not been widely determined. In addition, the relationships among preoperative imaging and surgical management, preoperative imaging, and TB delineation have been reported.[16,18] However, a comparison of tumor volumes derived from preoperative imaging, postoperative specimen analysis, and TB delineation has not been investigated. The aim of this study was to explore gross tumor volume (GTV) differences and correlations according to preoperative breast MRI, postoperative specimen analysis, and TB delineated using surgical clips for radiotherapy after BCS.

2. Materials and methods

2.1. Patients and selection

The female patients with pathology-proven breast cancer diagnosed between April 2014 and March 2015 and who were eligible for BCS were recruited. Enrolled patients underwent preoperative MRI and had clinical T1-2N0M0 stage cancers. Eligible patients included those who underwent lumpectomy and had tumor negative margins during a single operation. To improve the delineation accuracy and consistency, all of the enrolled patients had seroma clarity score of 3 to 5 and ≥ 5 surgical clips fixed to the central bottom and lateral edges of the excision cavity to mark the LC boundaries. Patients with a history of ipsilateral breast surgery and chest radiotherapy were excluded from the recruitment, patients with oncoplastic BCS were excluded from analysis, and patients who received neoadjuvant chemotherapy or neoadjuvant endocrine therapy were also excluded. This study was approved by the Institutional Review Board (Shandong Tumor Hospital Ethics Committee). Written informed consent was obtained from all patients.

2.2. Magnetic resonance imaging

MRI was performed using the Philips Achieva 3.0-T scanner (Amsterdam, Netherlands) with the THRIVE (T1 high-resolution isotropic volume excitation) acquisition technique. Patients were placed prone with the breasts positioned in a dedicated bilateral breast coil. The diagnostic MRI protocol began with preliminary imaging using fast-spin echo sagittal T2 with fat saturation and axial T1 sequences. This was followed by dynamic high-resolution simultaneous imaging of both breasts using the THRIVE sequence with 8 dynamic scans with fat saturation, performed after intravenous administration of a contrast agent (gadopentetate dimeglumine, 0.1 mmol/kg). Postprocessing consisted of 2 series of subtraction images. The subtraction images that were transferred to MIMvista version 6.1.0 (MIM Software; Cleveland, OH) software were 3 mm thick.

2.3. Specimen processing

The pathologists who evaluated the surgical specimens were blinded to the positions of the MRI-planned excision margins. Unfixed excised specimens (ES) were placed in a graduated cylinder, and GTV (GTV_{ES}) was determined using the Archimedes principle. The maximum length (cm), width (cm), and height (cm) of the tumor were measured by an experienced pathologist. The volume of tumor (GTV_{PAT}) was calculated using the following equation: $GTV_{PAT} = 1/6\pi \times \text{length} \times \text{width} \times \text{height}$.

2.4. Acquisition of computed tomography image sets

Before radiotherapy, all patients underwent a planning computed tomography (CT) scan in the supine position with the arms extended above the head. The standard CT simulation was acquired with a thickness of 3 mm using a 16-slice Brilliance Big Bore CT scanner (Philips Medical Systems, Inc.; Cleveland, OH). Subsequently, planning CT image sets were transferred to the Eclipse treatment planning system (Eclipse 8.6, Varian Medical Systems; Palo Alto, CA) for structure delineation.

2.5. Target volume delineation

Tumor volume (cm^3) according to MRI (GTV_{MRI}) was delineated by the same experienced radiologist using MIMvista software (MIM 6.1.0) with information from the preoperative MRI subtraction images. We also reconstructed the volume by adding a 1.0-cm margin around the GTV_{MRI} (GTV_{MRI+1}) to match the 1.0-cm margin routinely applied during surgery in our hospital.

To eliminate interobserver variation, the GTV_{TB} was contoured by the same breast irradiation oncologist specializing in radiation treatment of breast carcinoma with more than 5 years of radiotherapy experience in the Eclipse treatment planning system using the placement of the surgical clips as a guideline.

2.6. Statistical analyses

Because of non-normal distribution of variables, median values and ranges were used to describe the data. A Wilcoxon signed-rank test was performed to compare the paired tumor volume variables. Correlations were studied using the Spearman rank correlation coefficient. Statistical analyses were conducted using SPSS Statistics version 17.0 (Chicago, Illinois, America). All statistical tests were 2-sided, and P value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

There were 40 patients enrolled in our study. Seven patients were excluded from analysis because 3 patients were with oncoplasty and 4 patients received neoadjuvant chemotherapy or neoadjuvant endocrine therapy. The remaining 33 patients were eligible for further analysis. Patient and tumor characteristics are shown in Table 1. Most patients were diagnosed with an invasive ductal carcinoma with or without ductal carcinoma in situ (94%). Pathological stage was predominantly T1 (64%). All patients underwent lumpectomy. The average interval from lumpectomy to the planning CT scan was 91 days (range, 19–172 days).

3.2. Comparisons of gross tumor volumes

The median GTVs are shown in Table 2. GTV_{TB} was significantly larger than GTV_{MRI} or GTV_{PAT} or GTV_{MRI+1} ($P=0.000$, 0.000, and 0.007, respectively). There were no significant differences

Table 1

Patient characteristics.

Characteristic	Value (n=50)
Age, y	25–68
Median	45
Affected breast	
Left	28 (56%)
Right	22 (44%)
Histology	
Ductal carcinoma in situ	5 (10%)
Invasive ductal carcinoma	42 (84%)
Others	3 (6%)
Tumor location	
Outer upper quadrant	26 (52%)
Outer lower quadrant	6 (12%)
Inner upper quadrant	15 (30%)
Inner lower quadrant	3 (6%)

between GTV_{MRI} and GTV_{PAT}, or between GTV_{MRI+1} and GTV_{ES} ($P=0.188$ and 0.070, respectively). Furthermore, there was no significant difference between GTV_{ES} and GTV_{TB} ($P=0.264$). Figure 1 shows the distribution of volume and volume difference between GTV_{MRI} and GTV_{PAT} (Fig. 1A), between GTV_{MRI+1} and GTV_{ES} (Fig. 1B), between GTV_{ES} and GTV_{TB} (Fig. 1C), and between GTV_{MRI+1} and GTV_{TB} (Fig. 1D).

3.3. Correlations of gross tumor volumes

There was no significant correlation between GTV_{MRI} and GTV_{ES}, or between GTV_{MRI} and GTV_{TB}. Similarly, there was no significant correlation between GTV_{MRI+1} and GTV_{ES}, or between GTV_{MRI+1} and GTV_{TB}. Figure 2 shows the relationship between GTV_{ES} and GTV_{TB}. GTV_{ES} was positively related with GTV_{TB}.

The ratio of GTV_{ES} to GTV_{TB} represented the coincidence degree between GTV_{ES} and GTV_{TB}, and its median was 0.83. The relation between the ratio of GTV_{ES} to GTV_{TB} and the interval duration, number of surgical clips utilized, and primary tumors' locations were determined. The median number of surgical clips was 5 (range, 5–7). There were no significant correlations between the ratio of GTV_{ES} to GTV_{TB} and any of these factors ($P>0.050$ for all).

4. Discussion

For BCS, it is essential to obtain negative margins, as margin status is an important prognostic factor for local recurrence after breast-conserving therapy.[19] However, excising large masses of breast tissue could jeopardize cosmetic outcome and has not been shown to provide better local control or to improve overall survival rates.[20] Preoperative imaging-guided techniques were effective in improving the definition of the extent and localization of the tumor.[21] Furthermore, compared to postoperative EB-PBI, preoperative target volume delineation leads to considerably less interobserver variation.[22,23] Hence, in order to improve the balance between local control and cosmesis outcome, it is necessary to ascertain the extent of the tumor as accurately as possible by preoperative imaging.

MRI is currently used to evaluate disease extent for BCS, and its role in the evaluation of breast lesions is evolving. MRI has been shown to detect multifocal and multicentric cancers more often than conventional imaging.[11,24] Moreover, Bilimoria et al[25] evaluated the effect of breast MRI on clinical management and reported that 9.7% of women had a beneficial modification in surgical management based on preoperative breast MRI. Moreover, the rationale for preoperative MRI was that accurate delineation of the tumor extent might allow surgeons to achieve a negative resection margin during a single operation. Therefore, we performed a comparative study of volume relationships to evaluate the influence of preoperative MRI-based determination of tumor extent and target volume delineation on radiotherapy.

Several studies, utilizing various methods, have evaluated the accuracy of MRI for assessing tumor size and have shown a range of correlations between MRI and pathology.[26,27] In 100 (53%) patients with breast cancer tumors, Grimsby et al[27] reported that GTV_{PAT} and GTV_{MRI} were concordant within 0.5 cm. Similarly, there was no significant difference between GTV_{MRI} and GTV_{PAT} in the present study. Because of a lack of pathologic validation, diagnosing breast cancer lesions by MRI alone could produce false-positive or false-negative results.[28,29] In the present study, pathological analysis was performed to avoid false-positive or false-negative results, thereby validating the accuracy of MRI.

Although a few studies have investigated the accuracy of MRI to depict disease extent,[12,13] it is unclear how often surgeons perform surgery based on preoperative MRI-obtained parameters. In the present study, GTV_{MRI} was not significantly correlated with GTV_{ES}. Considering the fact that lumpectomy was performed with a circumferential margin of at least 1.0 cm,[30] we analyzed the relationship between GTV_{MRI+1} and GTV_{ES}. While there was no statistically significant difference between GTV_{MRI+1} and GTV_{ES}, they were not correlated with each other either. Because of non-normal distribution of variables, the standard deviation (SD) of GTV_{ES} (SD=15.30) was larger than GTV_{MRI+1} (SD=6.89). This result indicated that the distribution of GTV_{ES} was more discrete. As the accuracy of MRI was confirmed by pathological analysis, this seemingly contradictory finding can be explained by the fact that surgeons perform surgical excision according to their experience, and intersurgeon variability also plays a significant role. Moreover, because surgeons performed BCS randomly and radiation oncologists delineated GTV_{TB} according to the surgical clips placed in the LC, neither GTV_{MRI} nor GTV_{MRI+1} correlated with GTV_{TB}. Our results confirmed that the majority of surgeons performed BCS subjectively, ignoring imaging-guided diagnosis of tumor extent. Furthermore, in ES, the boundary of the primary tumor and surgical margin was anisotropic. Therefore, both surgeons and radiation oncologists should value the usefulness of

Table 2

Gross tumor volumes.

Volume	Median, cm^3	Range, cm^3
GTV_{MRI}	0.97	0.01–6.88
GTV_{PAT}	0.97	0.01–6.36
GTV_{MRI+1}	12.58	3.90–34.13
GTV_{ES}	15.46	1.15–70.69
GTV_{TB}	19.24	4.72–54.33

GTV_{MRI}, the tumor volume delineated based on preoperative MRI images; GTV_{PAT}, the tumor volume measured based on pathology; GTV_{MRI+1}, the tumor volume formed by adding 1.0-cm margin around GTV_{MRI}; GTV_{ES}, the tumor volume measured based on the excision specimen; GTV_{TB}, the tumor bed delineated based on surgical clips. GTV = gross tumor volume, MRI = magnetic resonance imaging.

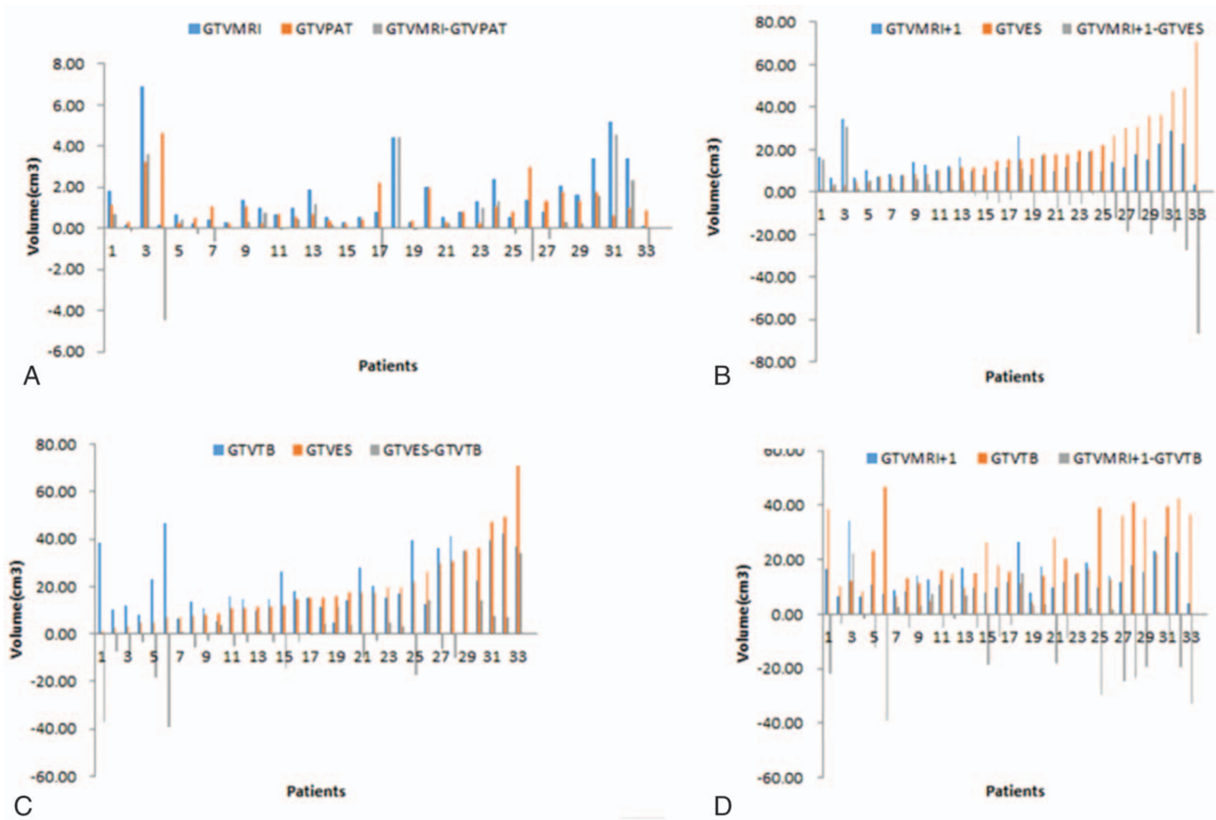

Figure 1. Distribution of gross tumor volume (GTV) and volume difference between (A) preoperative magnetic resonance imaging (GTV_{MRI}) and pathology (GTV_{PAT}), (B) extending 1.0-cm margin around the GTV_{MRI} (GTV_{MRI+1}) and excised specimens (GTV_{ES}), (C) excised specimens (GTV_{ES}) and tumor bed (GTV_{TB}), (D) extending 1.0-cm margin around the GTV_{MRI} (GTV_{MRI+1}) and tumor bed (GTV_{TB}).

preoperative MRI-guided techniques for surgical excision and GTV delineation.

Achieving accurate delineation of GTV_{TB} based on the LC size is critical for adequate local control in APBI. However, owing to breast density, the ability to visualize the LC is poor, and surgical clips and/or the seroma are therefore used to provide additional information on location.[31] Dzhugashvili et al[32] reported that the placement of surgical clips at lumpectomy enables visualization of the LC and improves the cavity visualization score on planning CT scans for APBI. However, there were no standard recommendations for the optimal number of markers to be implanted in the LC. Kirby et al[22] reported that 5 or more implanted markers are likely to be adequate for the purposes of TB delineation for partial breast/breast boost radiotherapy. Based on this, TB volumes were outlined using ≥5 clips in our study. When we compared the GTV_{TB}, delineated by surgical clips, to the GTV_{ES}, there was no significant difference, and GTV_{TB} correlated significantly with GTV_{ES} (Fig. 2). This indicates that placement of ≥5 surgical clips at the cardinal points of the LC is extremely useful for the LC visualization and accurate for TB delineation.

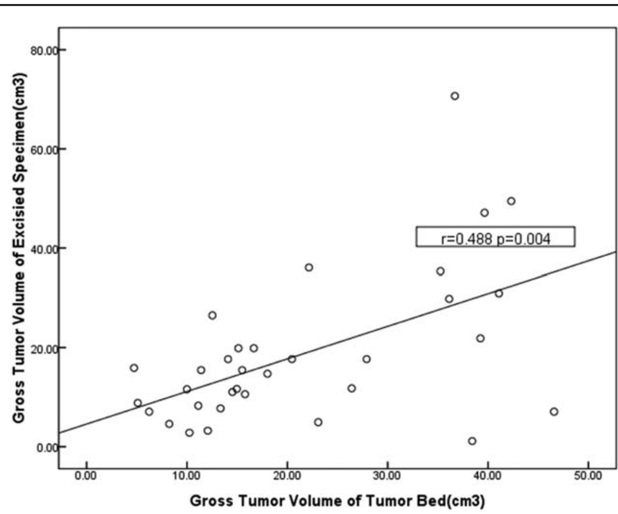

Figure 2. The relationship of gross tumor volume (GTV) between excised specimens (GTV_{ES}) and tumor bed (GTV_{TB}).

Previous studies have reported that an increased duration between surgery and radiotherapy caused a decrease in seroma clarity and LC volume; this affected the GTV_{TB}.[33,34] However, whether the use of surgical clips to delineate the GTV_{TB} has a similar effect was uncertain. Hurkmans et al[35] found that clip position could still change significantly after surgery, particularly when the initial seroma volume is large. Conversely, in the present study, the ratio of GTV_{ES} to GTV_{TB} was stable and was not affected by the length of duration between surgery and radiotherapy or the number of surgical clips used (for ≥5 clips). Furthermore, as a nonrigid tissue, the breast is deformed by gravity and breathing; therefore, the 3-dimensional movement correlations were asymmetrical. Hence, the location of the tumor according to breast quadrant might also influence the ratio of GTV_{ES} to GTV_{TB}. However, tumor location was not associated with the ratio of GTV_{ES} to GTV_{TB} in this study. Overall, because surgeons and radiation oncologists did not value the role of preoperative imaging-guided diagnosis of tumor extent, it is likely that these factors had no effect on the ratio of GTV_{ES} to GTV_{TB}.

If the accuracy of surgical resection could be improved by preoperative images, this is expected to further reduce the target volume for radiotherapy and result in a better cosmetic outcome alleviating postsurgical psychological stress. The potential limitation of this study is that it emphasized that most surgeons ignore imaging-guided diagnosis of tumor extent, but does not evaluate long-term outcomes in terms of local control and cosmesis outcome. Thus, in order to evaluate the usefulness of preoperative images in delineating tumor extent and TB, it is imperative that future studies should assess long-term results of ipsilateral breast tumor recurrences and cosmesis outcome.

5. Conclusion

Although preoperative MRI was available for every BCS patient, neither the volume of TB nor the volume of ES correlated significantly with the volume of tumor defined by the preoperative MRI. When ≥5 surgical clips were used to demarcate the LC during BCS, the volume of TB was consistent with the volume of ES. Therefore, a reasonably resected boundary of lumpectomy is a reliable indicator of the volume of TB. These data suggest that surgeons should strictly refer to preoperative images when performing surgical resections. Improving the accuracy of the volume of TB delineation can reduce the irradiated volume of normal breast tissue, achieving optimal oncologic and aesthetic outcomes.

References

[1] Fisher B, Anderson S, Bryant J, et al. Twenty year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
[2] Early Breast Cancer Trialists' Collaborative Group (EBCTCG)Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707–16.
[3] Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol 2007;25:3259–65.
[4] Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 2015;16:47–56.
[5] Offersen BV, Overgaard M, Kroman N, et al. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: a systematic review. Radiother Oncol 2009;90:1–3.
[6] Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 2009;74:987–1001.
[7] Yang TJ, Tao R, Elkhuizen PH, et al. Tumor bed delineation for external beam accelerated partial breast irradiation: a systematic review. Radiother and Oncol 2013;108:181–9.
[8] Njeh CF, Saunders MW, Langton CM. Accelerated partial breast irradiation using external beam conformal radiation therapy: a review. Crit Rev Oncol Hematol 2012;81:1–20.
[9] Polgár C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol 2013;108:197–202.
[10] Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol 2013;31:4038–45.
[11] Hata T, Takahashi H, Watanabe K, et al. Magnetic resonance imaging for preoperative evaluation of breast cancer: a comparative study with mammography and ultrasonography. J Am Coll Surg 2004;198:190–7.
[12] Uematsu T, Yuen S, Kasami M, et al. Comparison of magnetic resonance imaging, multidetector row computed tomography, ultrasonography, and mammography for tumor extension of breast cancer. Breast Cancer Res Treat 2008;112:461–74.
[13] Berg WA, Gutierrez L, NessAiver MS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology 2004;233:830–49.
[14] Schouten van der Velden AP, Boetes C, Bult P, et al. Magnetic resonance imaging in size assessment of invasive breast carcinoma with an extensive intraductal component. BMC Med Imaging 2009;9:5.
[15] Bedrosian I, Mick R, Orel SG, et al. changes in the surgical management of patients with breast carcinoma based on preoperative magnetic resonance imaging. Cancer 2003;98:468–73.
[16] Boersma LJ, Janssen T, Elkhuizen PH, et al. Reducing interobserver variation of boost-CTV delineation in breast conserving radiation therapy using a pre-operative ct and delineation guidelines. Radiother Oncol 2012;103:178–82.
[17] Onesti JK, Mangus BE, Helmer SD, et al. Breast cancer tumor size: correlation between magnetic resonance imaging and pathology measurements. Am J Surg 2008;196:844–8.
[18] Akashi-Tanaka S, Sato N, Ohsumi S, et al. Evaluation of the usefulness of breast CT imaging in delineating tumor extent and guiding surgical management: a prospective multi-institutional study. Ann Surg 2012;256:157–62.
[19] Lovrics PJ, Cornacchi SD, Farrokhyar F, et al. The relationship between surgical factors and margin status after breast-conservation surgery for early stage breast cancer. Am J Surg 2009;197:740–6.
[20] Tan MP, Sitoh NY, Sitoh YY. Perspectives of cosmesis following breast conservation for multifocal and multicentric breast cancers. Int J Breast Cancer 2015;2015:126793.
[21] Schmitz AC, van den Bosch MA, Loo CE, et al. Precise correlation between MRI and histopathology—exploring treatment margins for MRI-guided localized breast cancer therapy. Radiother Oncol 2010;97:225–32.
[22] Kirby AN, Jena R, Harris EJ, et al. Tumour bed delineation for partial breast/breast boost radiotherapy: what is the optimal number of implanted markers? Radiother Oncol 2013;106:231–5.
[23] van der Leij F, Elkhuizen PH, Janssen TM, et al. Target volume delineation in external beam partial breast irradiation: less inter-observer variation with preoperative-compared to postoperative delineation. Radiother Oncol 2014;110:467–70.
[24] Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248–58.
[25] Bilimoria KY, Cambic A, Hansen NM, et al. Evaluating the impact of preoperative breast magnetic resonance imaging on the surgical management of newly diagnosed breast cancers. Arch Surg 2007;142:441–5.
[26] Partridge SC, Gibbs JE, Lu Y, et al. Accuracy of MR imaging for revealing residual breast cancer in patients who have undergone neoadjuvant chemotherapy. AJR Am J Roentgenol 2002;179:1193–9.
[27] Grimsby GM, Gray R, Dueck A, et al. Is there concordance of invasive breast cancer pathologic tumor size with magnetic resonance imaging? Am J Surg 2009;198:500–4.
[28] Giess CS, Yeh ED, Raza S, et al. Background parenchymal enhancement at breast MR imaging: normal patterns, diagnostic challenges, and potential for false-positive and false-negative interpretation. Radiographics 2014;34:234–47.
[29] Shimauchi A, Jansen SA, Abe H, et al. Breast cancers not detected at MRI: review of false-negative lesions. AJR Am J Roentgenol 2010;194:1674.
[30] Rutgers EJ. Quality control in the locoregional treatment of breast cancer. Eur J Cancer 2001;37:447–53.
[31] Kirova YM, Castro Pena P, Hijal T, et al. Improving the definition of tumor bed boost with the use of surgical clips and image registration in breast cancer patients. Int J Radiat Oncol Biol Phys 2010;78:1352–5.
[32] Dzhugashvili M, Pichenot C, Dunant A, et al. Surgical clips assist in the visualization of the lumpectomy cavity in three-dimensional conformal accelerated partial-breast irradiation. Int J Radiat Oncol Biol Phys 2010;76:1320–4.

[33] Kader HA, Truong PT, Pai R, et al. When is CT-based postoperative seroma most useful to plan partial breast radiotherapy? Evaluation of clinical factors affecting seroma volume and clarity. Int J Radiat Oncol Biol Phys 2008;72:1064–9.
[34] Guo B, Li J, Wang W, et al. Interobserver variability in the delineation of the tumour bed using seroma and surgical clips based on 4DCT scan for external-beam partial breast irradiation. Radiat Oncol 2015;10:66.
[35] Hurkmans C, Admiraal M, Van der Sangen M, et al. Significance of breast boost volume changes during radiotherapy in relation to current clinical interobserver variations. Radiother Oncol 2009;90: 60–5.