# Tumor-to-Breast Volume Ratio as Measured on MRI: A Possible Predictor of Breast-Conserving Surgery versus Mastectomy

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**ABSTRACT:** **Background:** The surgical approach to breast cancer has changed dramatically in the past 20 years. The surgical objective today is to remove the tumor, ensuring negative margins and good cosmetic results, and preserving the breast when possible. Magnetic resonance imaging of the breast has become an essential imaging tool prior to surgery, diagnosing additional tumors and assessing tumor extent. Tumor-to-breast volume ratio, an important predictor of breast conservation, can be measured with MRI and may change the surgical decision.

**Objectives:** To measure the tumor-to-breast volume ratio using MRI in order to assess whether there is a correlation between this ratio and the type of surgery selected (breast-conserving or mastectomy).

**Methods:** The volumes of the tumor and the breast and the tumor-to-breast volume ratio were retrospectively calculated using preoperative breast MRI in 76 patients who underwent breast-conserving surgery or mastectomy.

**Results:** Breast-conserving surgery (lumpectomy) was performed in 64 patients and mastectomy in 12. The average tumor-to-breast volume ratio was 0.06 (6%) in the lumpectomy group and 0.30 (30%) in the mastectomy group ($P < 0.0001$).

**Conclusion:** The tumor-to-breast volume ratio correlated with the type of surgery. As measured on MRI, this ratio is an accurate means of determining the type of surgery best suited for a given patient. It is recommended that MRI-determined tumor-to-breast volume ratio become part of the surgical planning protocol for patients diagnosed with breast cancer.

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**KEY WORDS:** breast cancer, magnetic resonance imaging, tumor-to-breast volume ratio, breast-conserving surgery (BCS), mastectomy

The surgical approach to breast cancer has changed dramatically over the last 20 years. As a result of the randomized prospective trials that showed no statistically significant difference in the survival of patients who underwent mastectomy as compared to lumpectomy followed by radiation [1-4], most women diagnosed with breast cancer currently undergo breast-conserving therapy.

Moreover, local recurrence was shown to be low after BCT, estimated at 0.5%–1% per year, although this figure is still higher than the local recurrence rates following mastectomy [3-5]. The rate of recurrence is relatively higher among younger women and decreases over time [5]. The low local recurrence rate and the improvement of this parameter over time can be attributed, among other factors, to better preoperative breast imaging, adequate surgical margins, radiotherapy, and adjuvant systemic therapy [5-7]. Ensuring adequate surgical margins is fundamental to BCT [8], even in cases of ductal carcinoma in situ [9], but this is not always achieved and a considerable number of patients have involved margins and residual disease postoperatively [10] which require re-excision surgery or mastectomy.

Magnetic resonance imaging of the breast is another important diagnostic instrument in breast cancer. Its performance is indicated in several situations, including staging of the disease and treatment planning [11]. Many studies have demonstrated its superior sensitivity in assessing tumor size and detecting multifocal and multicentric disease [12-15]. MRI is also more accurate in detecting invasive lobular carcinoma [16] and due to its high rate of detection might have contributed to the higher incidence of this particular type of breast cancer observed in recent years [17].

Tumor-to-breast volume ratio is an important predictor of breast conservation and is one of the most crucial factors when predicting the cosmetic outcome. Since MRI of the breast enables an excellent assessment of the extent of disease, the tumor volume can be accurately measured. Furthermore, because it is a three-dimensional modality that is capable of scanning the entire breast, breast volume can also easily be measured and we reasoned that this modality could be applied for optimal measurement of the tumor-to-breast volume ratio. Our objective was to measure the tumor-to-breast volume ratio and to assess whether it correlates with the type

BCT = breast-conserving therapy

**Figure 1. [A]** Breast volume calculated by marking the borders of the affected breast in some axial images of breast MRI (arrow). The software completes the marking and calculates the breast volume (849 $cm^3$ in this case). **[B]** Tumor volume is provided by CAD imaging software with 1 cm margins, as seen in this sagittal image. Tumor-to-breast volume ratio is 0.329 (the tumor and 1 cm of free margins involve 32.9% of the breast). This patient underwent a mastectomy. The arrow indicates the tumor

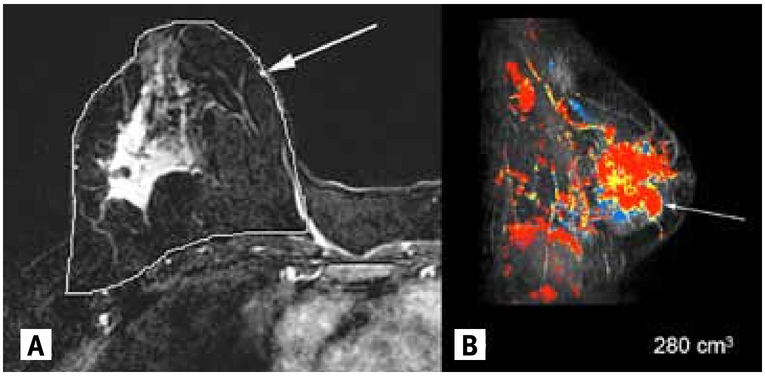
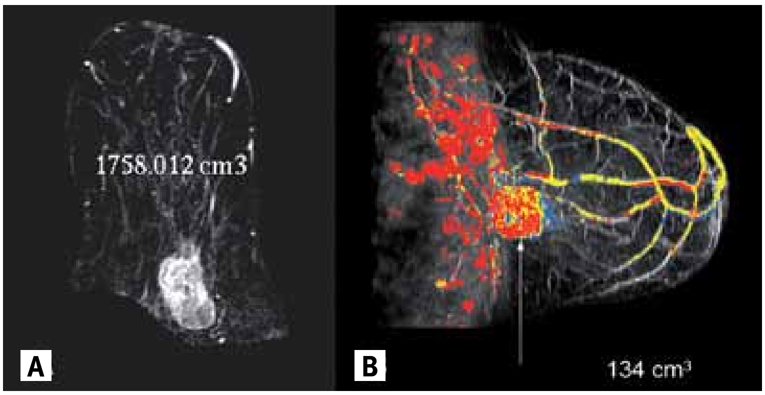



**Figure 2. [A]** Axial image of MRI of the breast in another patient, showing the breast volume measurement as explained in Figure 1A. The calculated breast volume is shown. **[B]** Tumor volume provided by CAD is shown here. The breast is very large, so the tumor-to-breast volume ratio is small – 0.076 (the tumor and 1 cm of free margins involve 7.6% of the breast). This patient underwent breast-conserving surgery. The arrow indicates the tumor




of surgery the patient underwent, either a breast-conserving surgery or a mastectomy.

## PATIENTS AND METHODS

We conducted a retrospective hospital-based study of 76 consecutive patients who were diagnosed with breast cancer and underwent preoperative breast MRI at our hospital between January 2008 and September 2010. These patients were referred for diagnostic contrast-enhanced MRI for the following reasons: a) assessment of disease extent, b) inconclusive findings by other imaging modalities or clinical examination, c) axillary lymphadenopathy without corroborating findings on mammography or ultrasound, or d) nipple discharge. Exclusion criteria were: a) *BRCA* gene carriers, b) if the decision to undergo mastectomy was based on the patient's request with no other medical indications, c) if the disease was multicentric, or d) patients whose disease was staged T4d. The study was approved by the institutional review board of our hospital.

### IMAGING PROTOCOL

Breast MRI was performed on a 1.5 T or 3 T clinical MR system (Signa® HDxt, GE Healthcare, Waukesha, WI, USA). Patients were placed in prone position in a dedicated 4 or 8 (respectively) channel VIBRANT™ breast array bilateral coil (GE Healthcare). The high spatial resolution scan protocol included axial 3D, T1-weighted sequences (ax Sen HR Vibrant Mask, TE/TR 2.7/5.5 ms, FOV 32x32 $cm^2$, flip angle 15°) one pre-contrast and 5 post-contrast, axial T2 Ideal (TE/TR 85/4180 ms, FOV 34x34 $cm^2$) with fat suppression, water suppression, in-phase and out-of-phase, and axial DWI (TE/TR 75.8/9500 ms, inversion time 160 ms, FOV 34x34 $cm^2$). The T1 scan was performed with a total of six dynamic acquisitions, one obtained before and five obtained immediately after administration of a bolus injection of 0.1 mmol/kg gadolinium (Gd-DOTA, Dotarem® 0.5 mmol/mL, Guerbet Asia Pacific, Hong Kong), followed by a 15 ml saline flush at an injection rate of 2 ml/sec using an automatic injector.

Maximum intensity projection reconstructions were performed at sagittal, axial and coronal planes. Enhancement evaluation and enhancement curves were performed in the CAD system (CADstream™, Confirma™, Kirkland, WA, USA).

### VOLUME MEASUREMENTS

The breast volume measurements were done using a semi-automated analysis. The breast volume was calculated in the AW workstation (AW VolumeShare™, GE Healthcare). We marked the borders of the breast at every 1.5 to 2.0 cm of breast scan, and the software completed the marking [Figures 1A and 2A].

Tumor volume was automatically calculated with CAD imaging software (CADstream™, Confirma™), based on summing voxels with an enhancement threshold of 70% over pre-contrast signal intensity. This volume measurement was previously proven to be reproducible and similar to other software with a high correlation to the histological specimen [18]. All the tumors included in the current study were determined as being malignant and confirmed by pathological examination after biopsy and surgical resection. Calculation of the tumor volume included a 1 cm free margin, which, ideally, should also be excised by the surgeon [Figures 1B and 2B]. The breast and tumor volumes were measured and the ratio between them calculated. When the tumor was multifocal, the volume measurement was performed using the semi-automated method in the AW workstation, in a similar manner as the breast volume measurement.

In patients who received neoadjuvant chemotherapy (n=16), we calculated the tumor volume according to the MRI on which the treatment decision was based, either pre- or post-NAC. In patients who received NAC and underwent lumpectomy, the post-treatment MRI was used to calculate the tumor-to-breast volume ratio. The pre-treatment MRI was used to calculate the tumor-to-breast volume ratio in cases of extensive disease that had not responded well to NAC treatment and as a result mastectomy was indicated. The MRI before treatment was also used to calculate the ratio in patients with extensive disease for which mastectomy was already planned irrespective of the response to NAC. The total volume of the lesions was calculated in cases of bi-lumpectomy.

All the data, including patients' demographics, neoadjuvant chemotherapy treatment, type of surgery, and pathological information were retrieved from the computerized patient records.

### STATISTICAL ANALYSIS

The average volumes of the tumors and breasts were calculated. The ratio between the volumes was calculated for each patient, as was the average of these ratios. The SAS for Windows version 9.2 *t*-test was used to assess the differences between the volumes and ratio (tumor and breast volumes and the tumor-to-breast volume ratio) between the groups. We set the value for statistical significance at $P < 0.05$.

## RESULTS

The study group comprised 76 patients. Characteristics of the group including the histological types of tumors are shown in Table 1. Sixty-four patients underwent breast-conserving surgery and 12 patients underwent mastectomy. In the breast-conserving group seven patients had bilateral lumpectomy and two patients bi-lumpectomy, with a total of 73 lumpectomies in 64 patients in this group. The most common tumor was invasive ductal carcinoma. Twenty-one percent of patients (n=16) received neoadjuvant chemotherapy, 17% (n=11) in the breast conservation and 41.6% (n=5) in the mastectomy group.

The average breast volume was 972 ml (range 236–2589 ml) in the BCS group and 976 ml (range 248–1545 ml) in the mastectomy group, and there was no statistically significant difference between them ($P > 0.05$). The average tumor volume (with 1 cm margins) in the mastectomy group of 292 ml (range 108–709.5 ml) was much larger than the average tumor volume in the BCS group, which was 52 ml (range 8–215 ml) ($P < 0.0001$).

The average tumor-to-breast volume ratio in the mastectomy group of 0.30 (range 0.15–0.54) was significantly higher than the average ratio of 0.06 (range 0.02–0.17) in the BCS group ($P < 0.0001$) [Figure 3]. The overlap between the groups was very small (0.15–0.17). Mastectomy was performed in all patients with more than 17% of involvement of the breast by the tumor, except for patients who received NAC and responded well and were therefore downgraded to breast-conserving surgery.

NAC = neoadjuvant chemotherapy
BCS = breast-conserving surgery

**Table 1.** Characteristics of the study population

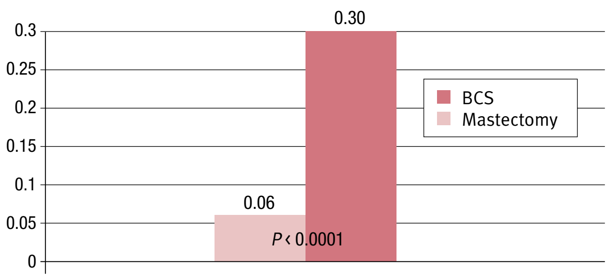
| | Breast-conserving surgery group* | | Mastectomy group | |
|---|---|---|---|---|
| | n | % | n | % |
| **Age at diagnosis (yr)** | | | | |
| ‹ 40 | 6 | 9.4 | 2 | 16.7 |
| 40–49 | 14 | 21.9 | 4 | 33.3 |
| 50–59 | 15 | 23.4 | 3 | 25 |
| 60–69 | 22 | 34.4 | 3 | 25 |
| ≥ 70 | 7 | 10.9 | – | – |
| Total no. of patients | 64 | 100 | 12 | 100 |
| **Pathology diagnosis** | | | | |
| IDC | 40 | 54.8 | 4 | 33.3 |
| ILC | 11 | 15 | 2 | 16.7 |
| IDC + DCIS | 9 | 12.3 | 3 | 25 |
| IDC + ILC | – | – | 1 | 8.3 |
| DCIS | 6 | 8.2 | 1 | 8.3 |
| LCIS | 1 | 1.4 | – | – |
| ILC + DCIS | 1 | 1.4 | 1 | 8.3 |
| ILC + LCIS | 1 | 1.4 | – | – |
| **Other**** | 4 | 5.5 | – | – |
| **Total no. of tumors** | 73 | 100 | 12 | 100 |

*64 patients in this group, including 7 bilateral lumpectomies and 2 bi-lumpectomies (total of 73 lumpectomies in the BCS group)

**Other: atypical medullary carcinoma of breast, micropapillary carcinoma, malignant high grade phyllodes tumor

IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, ILC = invasive lobular carcinoma

**Figure 3.** Comparison of tumor-to-breast volume ratios between the breast-conserving surgery and mastectomy groups




## DISCUSSION

Tumor-to-breast volume ratio is a highly informative parameter when deciding on the type of surgery for a given patient. This ratio is not routinely measured, and surgeons usually decide in a subjective manner on the type of operation to be performed.

IMAJ • VOL 16 • FEBRUARY 2014

Cosmetic results are reportedly worse when the volume of tissue excised is > 70–100 $cm^3$ [19, 20], but this will depend on breast size, how high the ratio is between the tissue excised and the breast volume, and the location of the tumor.

To the best of our knowledge, this is the first study to assess the tumor-to-breast volume ratio as measured on MRI and to correlate it to the type of surgery selected for the patient, i.e., breast conservation or mastectomy. This ratio has been shown to be a predictive factor of axillary lymph node metastases [21]. In the past, MRI-determined breast tumor volume was shown to be more predictive of recurrent-free survival than tumor diameter in patients undergoing neoadjuvant chemotherapy for breast cancer [22].

The results of this retrospective study demonstrate a direct correlation between this ratio and the type of surgery undergone. We reason that the MRI-derived volume ratio measurement can reliably select the optimal type of surgery for the patient. These MRI data have not been previously correlated to the type of surgery and, in our opinion, may serve to change the surgical decision from mastectomy to lumpectomy, primarily in cases of large tumors that responded well to neoadjuvant chemotherapy and of multifocal disease. According to our results, on average, the surgeon has to excise 6% of breast tissue (the tumor and an additional 1 cm margin) when BCT is indicated, and 30% when mastectomies are indicated (bearing in mind that excising ≥ 25% of breast tissue results in unacceptable deformity and poor cosmetic outcome).

Subjective observation of the tumor-to-breast volume ratio may lead to overestimation of this ratio and, subsequently, unnecessary mastectomies. With today's technology, when the volumes of tumors in other organs are calculated with sophisticated software, this practice should also be introduced in the setting of breast pathology. Additionally, the preservation of the breast also has an impact on body image and self-esteem. Highly accurate MRI measurements can be expected to spare a great number of mastectomies in favor of breast conservation.

It has been suggested that the introduction of breast MRI is linked to the increase in the rate of mastectomies [23,24]. This can be related to MRI's high sensitivity, showing additional lesions occult to mammography and ultrasound in the ipsilateral breast (and occult lesions in the contralateral breast) [23]. As a result¸ patients undergo a mastectomy that would not have been performed otherwise. The obvious theoretical advantage to the higher sensitivity of MRI is that it could reduce the need for re-excision among BCT patients and the likelihood of local recurrence, and even improve long-term survival, although evidence-based proof is lacking. It was recently demonstrated that MRI leads to decresead re-excision surgeries without a corresponding increase in mastectomies [25].

Although there is no difference in the mortality rates between BCT and mastectomies, Jatoi and Proschan's meta-analysis of randomized trials [1] showed that mastectomy significantly reduces the risk of locoregional recurrence. Those authors recommended that mastectomy with immediate breast reconstruction be considered for women with a high risk of local recurrence [1]. Indeed, the time may have come to reevaluate the locoregional recurrence rate, given the greater availability of breast MRI and the better preoperative assessment that it affords. We assume that adding the tumor-to-breast volume ratio in order to enhance the assessment may even help lower the recurrence rates.

We chose to measure the tumor volume together with 1 cm of free margins since the aim of BCT is complete excision of the tumor with clear margins [8] to prevent residual disease and locoregional recurrence. Kurniawan et al. [10] reported that 14% of patients who underwent BCS had involved margins, and that 17% of patients underwent at least one subsequent surgery (re-excision or total mastectomy). Dunne and co-authors [9] showed that negative surgical margins for DCIS should be obtained after BCS for DCIS. Calculating the tumor volume together with free margins provides more precise data for the surgeon who needs to excise sufficient tissue surrounding the tumor to obtain disease-free margins. Cosmetic results will also be better when the surgeon knows the exact dimensions that will yield those safe margins.

This study had several limitations: it was retrospective, the cohort was relatively small, and the imaging was performed with two different MRI systems. Furthermore, breast volume and multifocal tumor measurement were partially manual, which was time consuming, making this measurement impractical for routine use. Improvement in software would resolve this problem.

We conclude that the tumor-to-breast volume ratio, derived from MRI data, would help the surgeon decide between breast-conserving surgery and a mastectomy for a given patient. Additional prospective studies are needed to confirm our findings.

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DCIS = ductal carcinoma in situ

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## Capsule

### Perturbed neural activity disrupts cerebral angiogenesis during a postnatal critical period

During the neonatal period, activity-dependent neural-circuit remodeling coincides with growth and refinement of the cerebral microvasculature. Whether neural activity also influences the patterning of the vascular bed is not known. Whiteus et al. showed in neonatal mice that neither reduction of sensory input through whisker trimming nor moderately increased activity by environmental enrichment affects cortical microvascular development. Unexpectedly, chronic stimulation by repetitive sounds, whisker deflection or motor activity led to a near arrest of angiogenesis in barrel, auditory and motor cortices, respectively. Chemically induced seizures also caused robust reductions in microvascular density. However, altering neural activity in adult mice did not affect the vasculature. Histological analysis and time lapse in vivo two-photon microscopy revealed that hyperactivity did not lead to cell death or pruning of existing vessels but rather to reduced endothelial proliferation and vessel sprouting. This anti-angiogenic effect was prevented by administration of the nitric oxide synthase (NOS) inhibitor L-NAME and in mice with neuronal and inducible NOS deficiency, suggesting that excessive nitric oxide released from hyperactive interneurons and glia inhibited vessel growth. Vascular deficits persisted long after cessation of hyperstimulation, providing evidence for a critical period after which proper microvascular patterning cannot be reestablished. Reduced microvascular density diminished the ability of the brain to compensate for hypoxic challenges, leading to dendritic spine loss in regions distant from capillaries. Therefore, excessive sensorimotor stimulation and repetitive neural activation during early childhood may cause lifelong deficits in microvascular reserve, which could have important consequences for brain development, function and pathology.

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Eitan Israeli

**"Patience is also a form of action"**

Auguste Rodin (1840-1917), French sculptor, whose most well-known works are *The Thinker*, *The Kiss*, *The Burghers of Calais*, and the *Gates of Hell*