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ORIGINAL ARTICLE – BREAST ONCOLOGY

# Residual Breast Tissue after Mastectomy: How Often and Where Is It Located?

**M. Griepsma, MSc[1], D. B. W. de Roy van Zuidewijn, MD, PhD[2], A. J. K. Grond, MD, PhD[3], S. Siesling, PhD[4,5], H. Groen, MD, PhD[6], and G. H. de Bock[6]**

[1]Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [2]Department of Surgery, Medical Center Leeuwarden, Leeuwarden, The Netherlands; [3]Pathology Friesland, Leeuwarden, The Netherlands; [4]Department of Research and Registration, Comprehensive Cancer Centre The Netherlands, Utrecht, The Netherlands; [5]Department of Health Technology and Services Research, MIRA Institute of Technical Medicine and Biomedical Technology, University of Twente, Enschede, The Netherlands; [6]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

## ABSTRACT

**Background.** Residual breast tissue after a mastectomy can lead to a (second) primary breast cancer. The development of breast cancer after prophylactic mastectomy and the finding of normal breast tissue around a local recurrence support this assumption. The aim of the present study was to investigate the prevalence and localization of residual breast tissue after a mastectomy.

**Methods.** A series of 206 women who underwent a mastectomy between January 2008 and August 2009 in 11 hospitals were enrolled onto this study after written informed consent was obtained. From each mastectomy specimen, a total of 36 samples were obtained from the superficial dissection plane at predetermined locations. The biopsy samples were analyzed for the presence of benign breast tissue in the inked superficial area. Differences in percentage of positive samples were analyzed by generalized estimating equations to account for their interdependence.

**Results.** A total of 7,374 biopsy samples from 206 breast specimens of 206 patients were included in the analysis. In 76.2 % of the specimens ($n = 157$), one or more positive biopsy samples were found. The positive findings were found diffusely across the superficial dissection surface of the specimen with a significant predilection for the lower outer quadrant and the middle circle of the superficial dissection plane.

**Conclusions.** After a mastectomy, there is a high probability of residual breast tissue. This tissue is predominantly located in the middle circle of the superficial dissection plane and in the lower outer quadrant. Surgeons should be aware of these locations so they may remove as much of the benign breast tissue as possible.

The incidence of breast cancer in the world is high. In the Netherlands, 14,000 women are diagnosed with the disease each year. In spite of the increasing trend toward breast-conserving therapy, 41 % of the patients still receive a mastectomy.[1] Indications for a mastectomy are an extensive or multicentric carcinoma-in situ (ductal carcinoma-in situ, DCIS), a locally extensive breast carcinoma, the inability to achieve negative margins during breast-conserving surgery, the patient's wishes, and the prevention of breast cancer in women genetically predisposed to the disease.

After a bilateral prophylactic mastectomy, there is still a chance of developing breast cancer, a devastating event for the patient. In the literature, incidences are reported up to 1.9 %. Mastectomy reduces the risk of breast cancer by 85–95 %, but not by 100 %, suggesting that during the mastectomy, not all breast tissue had been removed.[2–12]

After therapeutic mastectomy, women have a risk of developing a local recurrence, ranging from 2.0 to 9.5 % with a median follow-up of 7 years.[13–23] Among the causes of local recurrence after mastectomy are lymphogenic spread, metastasis caused by inoculation, and incomplete

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D. B. W. de Roy van Zuidewijn, MD, PhD
e-mail: D.B.W.de.Roy.van.Zuidewijn@ZNB.nl

removal of the carcinoma. Another cause may be the occurrence of a new primary tumor in residual breast tissue. For the pathologist, it is not always possible to distinguish a local recurrence from a new primary breast cancer arising in residual breast tissue. Vaughan et al.[24] and Kim et al.[25] described residual breast tissue around a local recurrence, suggesting the development of the local recurrence from residual breast tissue.

To date, little is known about the prevalence and localization of residual breast tissue after mastectomy. So far only a few studies have been devoted to this issue. Most of these are old studies or are studies with a small number of breast specimens and/or biopsy procedures. The available studies agree that after any form of mastectomy, a small proportion of normal breast tissue is left behind (5–15 %).[13,26–31] The aim of the present study was to investigate how many patients have residual breast tissue after standard mastectomy procedures and to discover the exact localization of this residual breast tissue.

## MATERIALS AND METHODS

A series of women who underwent a mastectomy, for any reason, between January 2008 and August 2009 were enrolled onto this study. Male patients were excluded. All patients were verbally instructed about the study design, and signed informed consent was obtained after the operation. Approval to perform this multicenter histological study was obtained from the review board of the Medical Center Leeuwarden (the Netherlands).

The mastectomies were performed by 39 different surgeons from 11 different medical institutions in the north of the Netherlands. The inclusion time varied for the different hospitals. The aim of this study was to include a consecutive cohort of women per center. However, not all women were asked for inclusion, some did not provide informed consent, and some specimens were not available for the study because of damage during the operation or the pathologic process.

The surgeons used the following techniques: modified radical mastectomy, simple mastectomy (without axillary clearance), and skin-sparing mastectomy. In all cases, the nipple–areola complex was excised with the breast tissue. If present, the biopsy scar was included within the skin excision.

Each specimen was inked at the superficial dissection plane. For each specimen, a total of 36 samples were obtained from this area at previously determined locations (Fig. 1). Routine sections were cut at 2 μm, embedded in paraffin, and stained with hematoxylin and eosin. The sections were examined by light microscopy to evaluate the presence of normal breast tissue in the inked surface. A

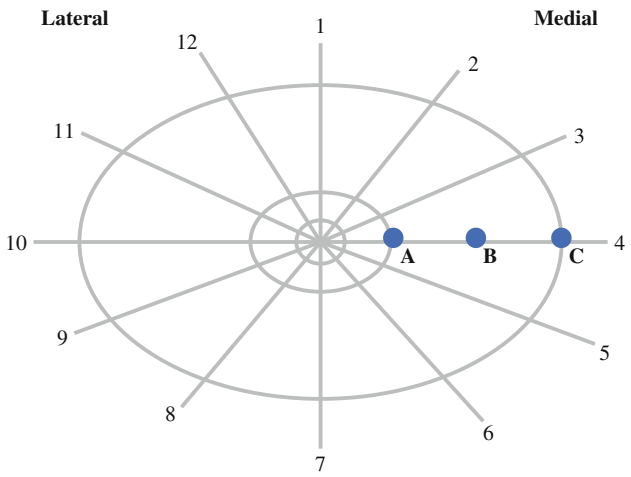


**FIG. 1** Previously determined biopsy locations. *A* skin margin, *B* between A & C, *C* margin with the fascia of the pectoral muscle

dissection plane was considered positive if breast tissue, instead of subcutaneous fat tissue, was located in the inked surface (Fig. 2a).

Data analyses were performed by SPSS statistical software. To assess how many resections leave residual breast tissue after standard mastectomy procedures, the percentage of specimens with any positive findings was determined. To assess the exact localization of this residual breast tissue, the percentage of positive findings of each of 36 predetermined biopsy locations (number of positive samples divided by the total number of samples) was calculated. Differences in percentage of positive biopsy samples per location were analyzed by generalized estimating equations to account for the nested data structure with multiple samples per patient. Differences between the different types of surgery (skin-sparing mastectomy, modified radical mastectomy, and simple mastectomy) in mean percentage of positive samples were calculated by the Kruskal–Wallis test. For all analyses, a two-sided *P* value of less than 0.05 was considered statistically significant.

## RESULTS

A total of 206 breast specimens from 206 patients were included. Of the intended number of 7,416 biopsy samples, 42 (0.57 %) samples could not be assessed because of damage to the specimen during the operation or the pathology process. Therefore, 7,374 samples were included in the analysis. The characteristics of the patients and the specimens are presented in Table 1. The mean and median age of the patients was 59 years (range 28–91 years). Sixteen patients (7.8 %) underwent formal skin-sparing mastectomy. All other patients underwent simple mastectomy or modified radical mastectomy. Most specimens

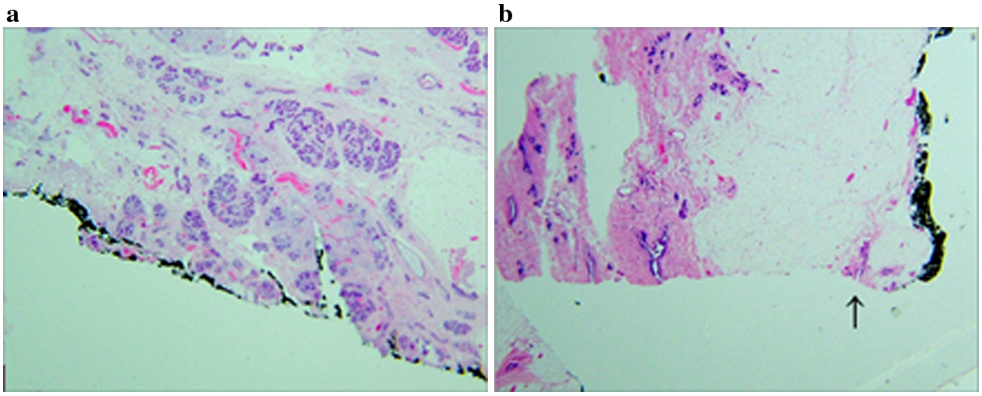


**FIG. 2** **a** Light micrograph showing the nonradical removal of breast tissue with mammary lobules in the inked margin. **b** Light micrograph illustrating the irregular distributions of mammary lobules within the breast tissue

contained a ductal type of breast cancer (75.9 %) with grade II disease (48.1 %). In 76.5 % of patients, an early stage breast cancer (T1–T2 tumor) was found, and 48.3 % of the patients had no positive lymph nodes (n0). The surgical margins involved tumor cells in five mastectomies (3.2 %).

In 76.2 % ($n = 157$) of the mastectomy specimens, one or more positive samples were found. Therefore, the resection was regarded as incomplete. The percentage of positive samples per specimen ranged from 1.0 to 61.1 %, with an average of 9.5 % and a median of 5.6 %. Between the different types of mastectomies, there was a significant difference in the mean percentage of positive samples: skin-sparing mastectomy 20.7 % ($n = 16$), simple mastectomy 8.8 % ($n = 124$), and modified radical mastectomy 8.2 % ($n = 66$) ($P < 0.000$).

Microscopic examination of our biopsy samples revealed no clear dissection plane between the breast tissue and the subcutaneous fat, with a quite irregular distribution of the mammary lobules (Fig. 2b). The positive samples were diffusely located across the superficial dissection plane of the specimen. The highest percentage of positive samples was found in the lower outer quadrant of the breast, at 14.8 %. This percentage was significantly higher than in the other quadrants (Table 2; Fig. 3a). In the middle of the superficial dissection plane (circle B), significantly more positive samples were found than in the central area (circle A, skin margin) and the outer dissection area (circle C, margin with the pectoral muscle), 12.1 versus 6.3 and 10.3 % (Table 3; Fig. 3b).

## DISCUSSION

To our knowledge, ours is the first study to describe the presence and localization of residual breast tissue after mastectomy. Benign breast tissue was found at the inked superficial dissection plane in 76.2 % (157 of 206) of the investigated specimens. The positive biopsy samples were found diffusely across the superficial dissection surface of the specimen with a significant predilection for the lower outer quadrant and halfway between the skin oval and the fascia of the pectoral muscle. This all suggests that normal breast tissue is left behind on the skin flap in most patients.

To date, only a small number of studies have addressed the issue of residual breast tissue after mastectomy. All studies agree that during any form of mastectomy, a small proportion of breast tissue is left behind (5–15 % of the total amount of breast tissue). The percentage of patients in whom this was found varies (21–59.6 %) and is lower than in our series (76.2 %).[13,26–31] This could be explained by the small number of specimens and biopsy samples in some of these studies: Barton et al. ($n = 55$, 6 samples per patient) and Tewari et al. ($n = 37$, 4 samples per patient) report residual breast tissue in, respectively, 21 and 25 % of patients.[29,30] Another explanation for this difference could be the origin of the samples. Cao et al.[13] and Torresan et al.[31] examined skin flaps for residual breast tissue after a skin-sparing mastectomy. The study of Cao et al. found residual breast tissue on the skin flap in 98 of 168 (53 %) patients and Torresan et al. in 25 of 42 (59.5 %) patients. The samples in our study were taken from the specimen and not from the patients' mastectomy cavity, consistent with the daily practice of pathologic examination in oncology. As a result of this strategy, the study had no influence on the patients and there was no increased risk of skin flap necrosis. Another reason for this method was the practical feasibility of the study because of the number of biopsy procedures and the number of patients. In addition, in most biopsy samples, there was no doubt about the fact that the surgeon had cut through benign breast tissue (Fig. 2a). Normal glandular ducts were seen in the inked surface. Another explanation could be the difference in knowledge of the surgeons about the study. In our study, the surgeons did not know about the study during the operation, so they could not have changed their operation

**TABLE 1** Characteristics of patients and specimens

| Characteristic | Value |
|---|---|
| Patients | |
| Age, y, mean (median) range | 59.0 (59.2) 28–91 |
| BMI, kg/m$^2$, mean (median) range | 26.2 (25.31) 15–42 |
| Premenopausal | 30.6 % (63/206) |
| Hormone therapy | 11.2 % (23/206) |
| History of breast cancer | 21.4 % (44/206) |
| Ipsilateral recurrence | 4.9 % (10/206) |
| Family history | 20.4 % (42/206) |
| Prophylactic | 8.3 % (17/206) |
| Therapy | |
| Neoadjuvant chemotherapy | 5.7 % (9/158) |
| Radiotherapy | 31.6 % (50/158) |
| Chemotherapy | 52.5 % (83/158) |
| Hormone therapy | 60.8 % (96/158) |
| Anti-Her-2 therapy | 7.6 % (12/158) |
| Specimens | |
| Pathology | |
| Invasive breast cancer | 76.7 % (158/206) |
| Pure DCIS | 9.7 % (20/206) |
| Benign | 8.7 % (18/206) |
| Recurrence | 4.9 % (10/206) |
| pT-stadium | |
| is | 11.2 % (20/178) |
| 1 | 40.5 % (72/178) |
| 2 | 36.0 % (64/178) |
| 3 | 9.0 % (16/178) |
| 4 | 3.4 % (6/178) |
| pN-stadium | |
| x | 5.1 % (9/178) |
| 0 | 48.3 % (86/178) |
| 1 | 27.0 % (23/178) |
| 2 | 12.9 % (23/178) |
| 3 | 6.7 % (12/178) |
| M-stadium | |
| 1 | 2.5 % (4/158) |
| Grade | |
| I | 13.9 % (22/158) |
| II | 48.1 % (76/158) |
| III | 36.1 % (57/158) |
| Unknown | 1.9 % (3/158) |
| Type | |
| Ductal | 75.9 % (120/158) |
| Lobular | 20.3 % (32/158) |
| Other | 3.8 % (6/158) |
| Tumor size, cm, mean (median) range | 2.75 (2.10) 0.0–10.0 |
| Side | |
| Left | 42.7 % (88/206) |
| Right | 57.3 % (118/206) |
| Tumor localization | |
| UIQ | 42.3 % |
| LIQ | 10.7 % |
| LOQ | 22.3 % |
| UOQ | 10.0 % |
| Central | 14.2 % |
| % positive lymph nodes, mean (median) range | 15 (0) 0–100 |
| Lymphovascular invasion | 43.4 % (36/83) |
| Extranodal spread | 28.9 % (24/158) |
| Nonradical | 3.2 % (5/158) |
| Multicentric | 9.5 % (15/158) |
| Receptors | |
| PR | 61.0 % (72/118) |
| ER | 73.1 % (114/156) |
| Her-2/Neu | 15.3 % (24/157) |

*UIQ* upper inner quadrant, *LIQ* lower inner quadrant, *LOQ* lower outer quadrant, *UOQ* upper outer quadrant, *DCIS* ductal carcinoma-in situ, *PR* progesterone receptor, *ER* estrogen receptor

technique. In conclusion, in most mastectomies, the surgeon leaves benign breast tissue behind.

What is the explanation for residual breast tissue after a mastectomy? Investigating our specimens showed no clear dissection plane between the breast tissue and the subcutaneous fat (Fig. 2b). The closer to the skin, the lower the density of breast tissue becomes. In addition, the superficial fascia of the breast was not always clearly visible. In 2002, Beer et al. wrote about this superficial fascia. The fascia was absent in 44 % of resection specimens. When the fascia was present, 42 % of specimens contained several islands of breast tissue within the fascia. The minimal distance between the fascia and the dermis varied from only 0.2–4.0 mm, which means that the fascia is too superficial to use as a landmark for dissection because the resulting flap may be too thin.[32] These findings probably provide an anatomic basis for the observed difficulty in removing all the breast tissue during a skin-sparing mastectomy. Another explanation could be a greater surface of breast tissue than expected. In 1940, Hicken et al. [26] analyzed 358 mammograms after contrast had been injected into the duct. They noted that breast tissue was widely distributed over the entire anterolateral aspect of the chest wall with extensions into the axilla, the epigastric space, and beyond the anterior borders of the latissimus dorsi muscle.

The largest number of positive biopsy samples in our study were found in the lower outer quadrant of the breast

**TABLE 2** Differences in distribution of positive biopsy findings per quadrant

| Quadrant | % (*n* positive/*N* total) 95% CI | Simple | MRM | SSM | *P* value for | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | UIQ | LIQ | LOQ | UOQ |
| UIQ (1–3) | 7.4 (137/1852) 6.21–8.60 | 6.8 % | 5.6 % | 19.4 % | – | 0.059 | **<0.001** | 0.976 |
| LIQ (4–6) | 9.3 (171/1845) 7.95–10.59 | 10.0 % | 5.7 % | 18.1 % | 0.059 | – | **<0.001** | **0.030** |
| LOQ (7–9) | 14.8 (272/1844) 13.13–16.37 | 12.7 % | 15.0 % | 29.6 % | **<0.001** | **<0.001** | – | **<0.001** |
| UOQ (10–12) | 6.9 (126/1833) 5.72–8.03 | 5.8 % | 6.7 % | 16.1 % | 0.976 | **0.030** | **<0.001** | – |

For the total number of biopsy samples, all samples belonging to the relevant quadrant were added. Generalized estimating equations were used to calculate the findings. Bold *P* values are significant

*CI* confidence interval, *UIQ* upper inner quadrant, *LIQ* lower inner quadrant, *LOQ* lower outer quadrant, *UOQ* upper outer quadrant, *Simple* simple mastectomy, *MRM* modified radical mastectomy, *SSM* skin-sparing mastectomy

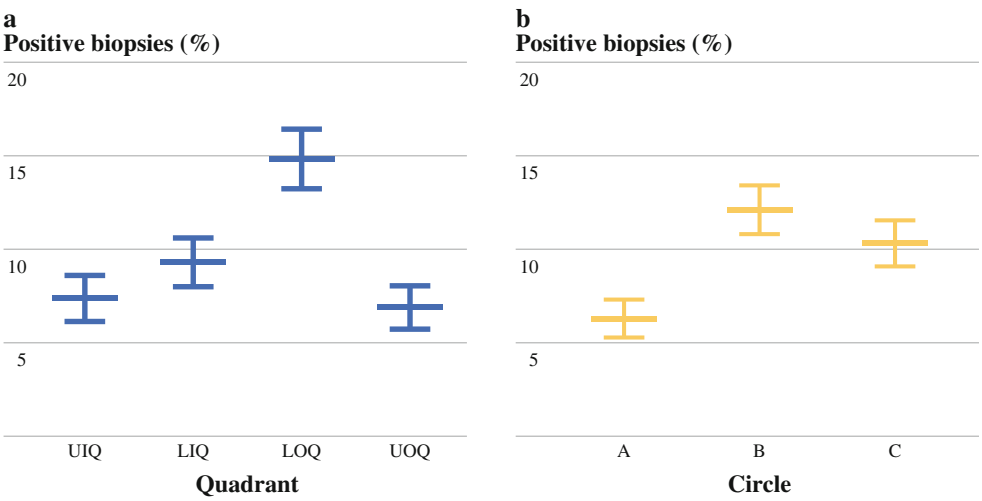


**FIG. 3** Distribution of positive biopsies

**TABLE 3** Differences in distribution of positive biopsy samples per circle

| Circle | % (*n* positive/*N* total) 95 % CI | Simple | MRM | SSM | *P* value for | | |
|---|---|---|---|---|---|---|---|
| | | | | | A | B | C |
| A | 6.3 (155/2469) 5.32–7.24 | 4.6 % | 4.4 % | 13.0 % | – | **<0.001** | **0.001** |
| B | 12.1 (297/2447) 10.84–13.43 | 12.2 % | 10.0 % | 20.5 % | **<0.001** | – | **0.006** |
| C | 10.3 (254/2458) 9.13–11.54 | 9.0 % | 9.3 % | 25.1 % | **0.001** | **0.006** | – |

For the total number of biopsy samples, all samples belonging to the relevant quadrant were added. Generalized estimating equations were used to calculate the findings. Bold *P* values are significant

*CI* confidence interval, *A* skin margin, *B* ½A–C, *C* margin with the fascia of the pectoral muscle, *Simple* simple mastectomy, *MRM* modified radical mastectomy, *SSM* skin-sparing mastectomy

specimen. An explanation for the lower outer quadrant as the predilection site for residual breast tissue is not straightforward. None of the aforementioned studies looked for the precise location of this residual breast tissue, so no comparison exists. Perhaps the surgeons paid more attention to the upper outer quadrant; most surgeons regarded this as the most difficult quadrant in which to achieve complete resection. As a result, they were able to excise all the breast tissue in this location. Another explanation could be a difference in the thickness of the subcutaneous fat between the quadrants. If the subcutaneous layer is thinner in the lower quadrants, it would be more difficult to create a skin flap without benign breast tissue in it.[31]

Residual breast tissue after mastectomy may give rise to a (secondary) breast cancer. At present, to our knowledge, no studies have looked at a direct relationship between residual breast tissue and the development of a new breast cancer. The development of a primary breast cancer after a bilateral prophylactic mastectomy suggests such a relationship.

Although the incidence of breast cancer after prophylactic mastectomy is low, case reports describe patients who developed invasive breast cancer after this type of surgery.[2–4] The incidence varied from 0 to 1.9 %.[5–12] Although bilateral prophylactic mastectomy reduces the risk of breast cancer by 85–95 %, this risk has not yet dropped to zero. Also, the aforementioned studies suggest a relationship between residual breast tissue and the development of a new breast cancer. Local recurrence rates are associated not only with residual breast tissue left by inadequate surgical techniques but also with factors such as tumor stage, tumor grade, young age, and lymphovascular invasion.[33] For this reason, it is sometimes suggested that the contribution of the surgical technique will have little impact. Torresan et al.[31] and Cao et al.[13] however, demonstrated residual disease in the skin flaps in, respectively, 9.3 and 8.3 % of their patients.[13,31] This residual disease could be associated with local recurrence, i.e., related to surgical techniques and not to tumor-related prognostic factors. In addition, the studies by Vaughan et al. and Kim et al. described residual breast tissue around the local recurrence, suggesting the development of the local recurrence from this residual breast tissue. Vaughan et al. identified residual breast tissue in 2 of 11 recurrence specimens.[24] Kim et al. described 10 patients in whom local recurrence developed after a total mastectomy for DCIS. Five out of 10 patients had normal breast tissue around the local recurrence, suggesting that the surgeon had not completely removed the breast tissue. The remaining tissue may have contained occult intraepithelial disease, or a de novo invasive cancer may have developed in this tissue. Data from Kim et al.[25] suggest that patients are more likely to experience local recurrence after multiquadrant DCIS or when there is residual tissue after a mastectomy.

Given the above considerations, our patients will be followed for 5–10 years to see whether the patients with more positive biopsy samples have a greater risk of developing a (second) primary breast cancer. Because the precise locations of the positive samples are recorded, development of a (secondary) primary or a local recurrence can be related to this location. In the meantime, it is important to inform every patient, but especially patients who undergo bilateral prophylactic surgery, about the sizable risk of leaving a small amount of residual breast tissue after a mastectomy. Therefore, they have a small but realistic risk of developing invasive breast cancer or DCIS in this residual breast tissue. This is especially true for young patients with a known gene mutation for or a family history of breast cancer. Not only do they have a greater risk of developing breast cancer, but they also have many more years in which to develop it. In these patients, the surgeon should pay additional attention to the lower outer quadrant during the mastectomy to remove as much of the benign breast tissue as possible.

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