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# Clinical outcomes of 1,578 Chinese patients with breast benign diseases after ultrasound-guided vacuum-assisted excision: recurrence and the risk factors

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**KEYWORDS:**
Breast benign diseases;
Ultrasound-guided vacuum-assisted excision;
Risk factors;
Recurrence;
Re-excisions

**Abstract**

**BACKGROUND:** The aim of this study was to evaluate the clinical outcomes of 1,578 patients with breast benign diseases after excisions and the risk factors.

**METHODS AND RESULTS:** With a median follow-up of 34 months, 69 patients were identified to have recurrence (local recurrence: 45; new lesion: 24). Univariate and multivariate analyses revealed that multiple lesions, a larger lesion size, and a hematoma were independent risk factors for recurrence. Patients with in situ recurrence tended to have fewer lesions and more samples taken per lesion. Patients with new lesions tended to have multiple lesions. After re-excisions, there was no second recurrence events observed in the patients with local recurrence (0/30), whereas 5 patients with new lesions (5/14) were noted to have second recurrence events.

**CONCLUSIONS:** Ultrasound-guided vacuum-assisted biopsy for the complete excision of breast benign diseases is safe and effective. Local recurrence and new lesions may have different clinicopathological features and underlying mechanisms. Different management might be given to patients with a different pattern of recurrence.



Breast benign diseases have a much higher incidence than breast cancer.[1–3] Generally, women with benign breast disease might not have an increased risk of developing breast cancer.[4–7] Therefore, the conservative management such as periodic examinations for these lesions is widely accepted among clinical practitioners. However, many patients may prefer complete excisions for these lesions, partially because of the psychologic stress concerning the potential malignant transformation. The rapid progress of the minimal invasive diagnostic tools is another reason. Introduced in the late 1990s,[8] vacuum-assisted biopsy (VAB, Mammotome Johnson & Johnson, Cincinnati) has become a major tool for evaluating breast lesions.[9] With the advent of large-bore cannulae, the VAB device greatly prompted the complete excision of breast lesions in our daily practices.[10]

To our knowledge, there are few studies focusing on the recurrence of breast benign diseases after complete exci-

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sions. Grady et al[11] reported that the overall recurrence rate was 15% in patients with percutaneous excisions of fibroadenoma after a median follow-up of 22 months. They showed that the initial lesion size was an independent predictor for fibroadenoma, which was also confirmed by Kim et al.[12] However, less than 100 patients were included in their studies. They also did not incorporate the lesion number of each patient into analysis, which might be a strong predictor for recurrence. Furthermore, they failed to mention the appropriate management for these patients with recurrent benign disease. Shall we continue a second excision or just simply put them under close surveillance? More comprehensive studies are in need.

In this study, we retrospectively reviewed the clinical outcomes of 1,578 patients who underwent complete excisions of the benign lesions in our institution. Risk factors for predicting the recurrences were analyzed. We proposed for the first time that recurrent events can be categorized into local recurrences and new lesions, which may have clinical implications for surgeons.

## Methods

### Patients

This study was approved by the institutional review board. Between 2007 and 2009, 1,578 patients with a diagnosis of breast benign diseases through UGVAB were included in this study. Clinicopathological features of these patients were collected. Patients meeting one of the following were excluded: (1) women with lesions that were suspected or pathologically proved to be malignant; (2) women with coagulation abnormalities, nipple discharge, organ dysfunction, or an allergy to local anesthesia; and (3) women with the existence of some physical or psychological condition that might interfere with the operation or follow-up.

### Procedure

Before the UGVAE, data on lesion character were confirmed by ultrasound imaging. Then, shadow casting was used to mark the lesion on paper in geometric proportion, which was used to judge whether the possible recurrence later was in situ or not. For the excision procedure, 2 experienced breast surgery specialists managed the procedure. One surgeon specialized in ultrasonic guidance (2 years of specialized training), and the other was in charge of surgical procedures. Both surgeons had a color Doppler flow image license. Ultrasonic guidance was performed using equipment with linear array transducers with variable frequencies and a range of 8 to 11 MHz (LogiQ book XP; GE). Once the target lesion was identified and noted, local anesthetic was administered. The 8G Mammotome was then inserted into the area under the lesion and properly positioned under ultrasound guidance. The vacuum line drew breast tissue through the aperture of the probe, the rotating cutting device was advanced, and tissue samples were collected via the tool's suction mechanism. Lesions were regarded as being completely excised when no residual lesion could be detected in ultrasonic imaging or in the last several samples. In cases in which the lesion was completely excised, multidirectional excision was necessary, and multiple specimens could be collected. The surgeon rotated the longitudinal axis of the probe, moving the sampling chamber approximately 45° to its new position. This entire cycle was repeated until all desired areas had been sampled. If the lesion size was more than 2.5 cm, the probe was moved forward or backward as needed. Hematocele and air were extruded out of the cavity at the end of the procedure. The incision was then sutured without drainage. Cavities were compressed with balled-up gauze and then wrapped with plastic bandages. A pathology report was completed for each lesion, and primary were recorded. Patients' final pathology results were usually classified at their highest risk level according to the classification scheme of Page et al[13] (ie, nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasias). Procedural pain and postprocedural pain were evaluated by a visual analog pain rating scale ranging from 0 to 10. A score of 4 to 10 was defined as a pain event. Procedural bleeding was defined as having a blood suction volume of more than 10 mL, continuous bleeding with compression for more than 2 minutes, or hematoma development during the procedure.

Patients were scheduled for follow-up at 48 hours, 1 month, and every 6 months after the procedure. All the patients were clear of palpable lesions or ultrasound-detected lesions within 1 month after UGVAE. Hematoma was defined as a clinically palpable mass with a visible hypoechoic area by ultrasound. Fine needle biopsy to withdraw blood is necessary for the diagnosis of a hematoma. Recurrence events were defined as the presence of clinically palpable masses or the evidence of lesions from the ultrasound. Patients who experienced recurrence events were required to undergo re-excision. The location of the recurrence was compared with the previous lesions recorded by the shadow-casting procedure before the initial treatment. Local recurrence and new lesions were defined as benign diseases that reoccurred near and away from the original lesion location, respectively.

### Statistical methods

A comparison of clinicopathological features between patients with and without recurrence and between patients with local recurrence and new lesion was performed with the chi-square test. Univariate and multivariate analysis of risk factors for recurrence were performed with Kaplan-Meier and Cox-regression analysis, respectively. Age, lesion number, number of samples taken per lesion, pathology, distance to the nipple-areola complex, lesion size, procedural pain, procedural bleeding, ecchymosis, and hematoma were included in the risk factor analysis. Statistical

**Table 1** Clinicopathological features

| | n | % |
|---|---|---|
| Age | | |
| ≥35 y | 845 | 53.5 |
| <35 y | 733 | 46.5 |
| Number of lesions | | |
| Multiple lesions (≥2) | 882 | 55.9 |
| Single lesions | 696 | 44.1 |
| Samples taken per lesion* | | |
| ≥5 samples per lesion | 787 | 49.9 |
| <5 samples per lesion | 791 | 51.1 |
| Pathology | | |
| Fibroadenoma | 1,243 | 78.8 |
| Other benign diseases | 335 | 21.2 |
| Distance to the nipple-areola complex | | |
| ≥2.5 cm | 685 | 43.4 |
| <2.5 cm | 893 | 56.6 |
| Ultrasound size† | | |
| ≥1 cm | 916 | 58 |
| <1 cm | 662 | 42 |

*Excision times per lesion = total excision times per number of lesions.

†The maximum dimension diameter was used.

tests were 2 sided. All statistical analyses were run using SPSS version 17.0 (SPSS Inc, Chicago, IL).

## Results

### Patient demographics and lesion parameters

A total of 3,854 lesions were collected from 1,578 patients with a median age of 35 years (range 12–72 years). The mean size of those lesions detected by ultrasound was 1.24 cm (range .4–5.6 cm). The number of lesions, the number of samples taken per lesion, the distance to the nipple-areola complex, and ultrasound size are summarized in Table 1. Over 97% patients are satisfied with their cosmetic results. No patients experienced infection after the procedure. Histology of the removed lesions included fibrocystic change (234 cases, 14.8%), fibroadenoma (1243 cases, 78.7%), apocrine metaplasia (17 cases, 1.1%), papilloma (35 cases, 2.2%), and others (49 cases, 3.1%).

Procedural complications including bleeding (>10 mL) and pain (visual analog scale score >4) were reported in 472 (472/1,578, 29.9%) and 435 (435/1,578, 27.6%) patients (Table 2). Postprocedural complications were also summarized in Table 2. Postprocedural pain (visual analog scale score >4) was reported by 430 patients (430/1,578, 27.2%) and ceased within 6 months after the procedure. We also observed ecchymosis in 210 patients (210/1,578, 13.3%) and hematomas in 116 patients (116/1,578, 7.4%). Postprocedural nipple discharge was scarce, occurring in only 31 patients (31/1,578, 1.9%), all of which cleared up in 6 months. Other postprocedural complications included 11 cases of skin depression (11/1,578, .7%), 18 cases of dysthitia (18/1,578, 1.1%), 4 cases of skin tear (4/1,578, <1%), and 1 case of local anesthetic intoxication (1/1,578, <1%).

### Clinical outcomes and the risk factors

In total, 31 (31/1,578, 1.9%) local recurrence and 17 (17/1,578, 1.1%) new lesion cases were observed with a median follow-up of 34 months (18–76 months). Univariate analysis revealed that patients with multiple lesions (≥2, $P < .01$), larger-sized lesions detected by ultrasound (≥1 cm, $P < .01$), or a postprocedural hematoma ($P < .01$) had a significantly higher crude recurrence rate. Multivariate analysis revealed that multiple lesions (hazard ratio [HR] = 1.7; 95% confidence interval [CI], 1.0–3.0; $P < .01$), a larger lesion size (HR = 2.2; 95% CI, 1.3–3.8; $P < .01$), and the presence of a postprocedural hematoma (HR = 3.0; 95% CI, 1.6–5.5; $P < .01$) independently predicted the recurrence events (Table 3).

### Clinicopathological features of patients with local recurrence or new lesions and their management

The clinicopathological features of patients with local recurrence or a new lesion are reviewed. Patients with local recurrence have fewer lesions ($P < .01$), more samples taken per lesion ($P < .01$), and absence of procedural bleeding ($P < .01$) when compared with patients with new lesions. The distribution of age, pathology, and distance to the nipple is similar between patients with local recurrence and new lesions.

In total, 30 of 45 local recurrence cases and 15 of 24 new lesion cases received re-excision. The pathology subtypes of these recurrent diseases were nearly identical to their primary ones. After a median follow-up of 16 months (range 6–35 months), no more events were observed in the local recurrence cases, whereas 5 new lesions were found in the new lesion cases (Table 4).

**Table 2** Procedural and postprocedural complications and the risk factors

| | n | % |
|---|---|---|
| Procedural complications | | |
| Procedural pain | 472/1,578 | 29.9 |
| Procedural bleeding | 435/1,578 | 27.6 |
| Postprocedural complications | | |
| Postprocedural pain | 430/1,578 | 27.2 |
| Ecchymosis | 210/1,578 | 13.3 |
| Hemotoma | 116/1,578 | 7.4 |
| Skin depression | 11/1,578 | .7 |
| Nipple discharge | 31/1,578 | 2 |
| Difficulty in breastfeeding | 18/320 | 5.6 |
| Skin tear | 4/1578 | .2 |

**Table 3** Univariate and multivariate analysis: independent risk factors for recurrence events

| | Univariate analysis | Multivariate analysis | | |
|---|---|---|---|---|
| | *P* value | HR | 95% CI | *P* value |
| Lesion number: multiple vs single | <.01 | 1.7 | 1.0–3.0 | .049 |
| Lesion size: ≥1 vs <1 cm | <.01 | 2.2 | 1.3–3.8 | <.01 |
| With hematoma | <.01 | 3 | 1.6–5.5 | .01 |

Kaplan-Meier survival analysis and Cox regression analysis were used for univariate and multivariate analysis, respectively.

## Comments

Generally, women with benign breast disease had no greater risk of developing breast cancer than other women.[4–7] Conservative treatment including close surveillance is the standard therapy. However, Hartmann et al[14] reported that benign diseases did increase the risk of breast cancer. Their results were further confirmed by Worsham et al.[15] The existence of those abnormal lesions may arouse psychological stress for some of the patients. Therefore, more and more patients prefer complete excision of these lesions through a minimally invasive way. The final pathology report of their lesions may largely eliminate their concerns. In our daily practices, we noticed patients may consult about the recurrent rate of their benign diseases if complete excision was performed. To our knowledge, there are few studies concerning the clinical outcomes of patients with benign diseases after excision. The reported overall recurrence rate ranged from 15% to 39%.[11,12,16,17] Our recurrence rate was significantly lower than the previous ones. All the Mammatome probes we used were 8-G, whereas some of the probes were 11-G in the reported studies. Probes with a larger core may achieve disease clearance more easily. Another reason for our lower recurrence rate might be the relatively short follow-up time. In the study by Kim et al,[12] all of their enrolled patients had at least a 2-year follow-up.[12] The median follow-up time of our study is 34 months, which is higher than the follow-up time in Grady et al's study.[11]

Grady et al[11] and Kim et al[12] also reported that the lesion size was an independent risk factor for recurrence. However, their sample size was not large enough. A logistic regression model was used in their studies for identifying risk factors. In our view, we believed that the Cox regression HR model was more suitable for multivariate analysis because it incorporated the follow-up time of each patient into the analysis. In addition, they failed to include the lesion number in their multivariate analysis for recurrence. In our study with 1,578 patients, we used the Cox regression model and confirmed that a larger lesion size (≥ 1 cm) detected by ultrasound independently predicted the recurrence. Furthermore, we noted the lesion number of each patient (multiple vs single) and the occurrence of a postoperational hematoma were independent predictors for compromising clinical outcomes. It is possible that the patients with multiple lesions had microenvironment or genetics that are prone to develop breast benign diseases. Therefore, the recurrence rate may be much higher in these patients. A hematoma is a common postprocedural complication.[18] It is difficult to understand the correlation between a hematoma and recurrence events. Patients with a larger lesion size and multiple lesions are more likely to have a hematoma as a postprocedural complication. This relationship partially explained this interesting observation. A hematoma may possibly work as a reservoir for reserving residual abnormal cells, which may be potential causes for recurrence.

**Table 4** Pathology distribution and follow-up of patients after a second procedure for re-excisions of recurrence events (local recurrence and new lesions)

| Pathology | Patients with recurrence | Patients received re-excision | Pathology distribution after re-excisions | Numbers of patients with second recurrence after the re-excisions |
|---|---|---|---|---|
| Local recurrence | | | | |
| Fibrocystic change | 5 | 2 | 2 | 0 |
| Fibroadenoma | 38 | 26 | 28 | 0 |
| Calcification | 1 | 1 | 0 | 0 |
| Sclerosing adenosis | 1 | 1 | 0 | 0 |
| New lesions | | | | |
| Fibrocystic change | 1 | 1 | 2 | 0 |
| Fibroadenoma | 22 | 13 | 12 | 5* |
| Papilloma | 1 | 1 | 1 | 0 |

*All of these 5 patients received a third operation, and the pathology assessment revealed that all of them were still having fibroadenoma.

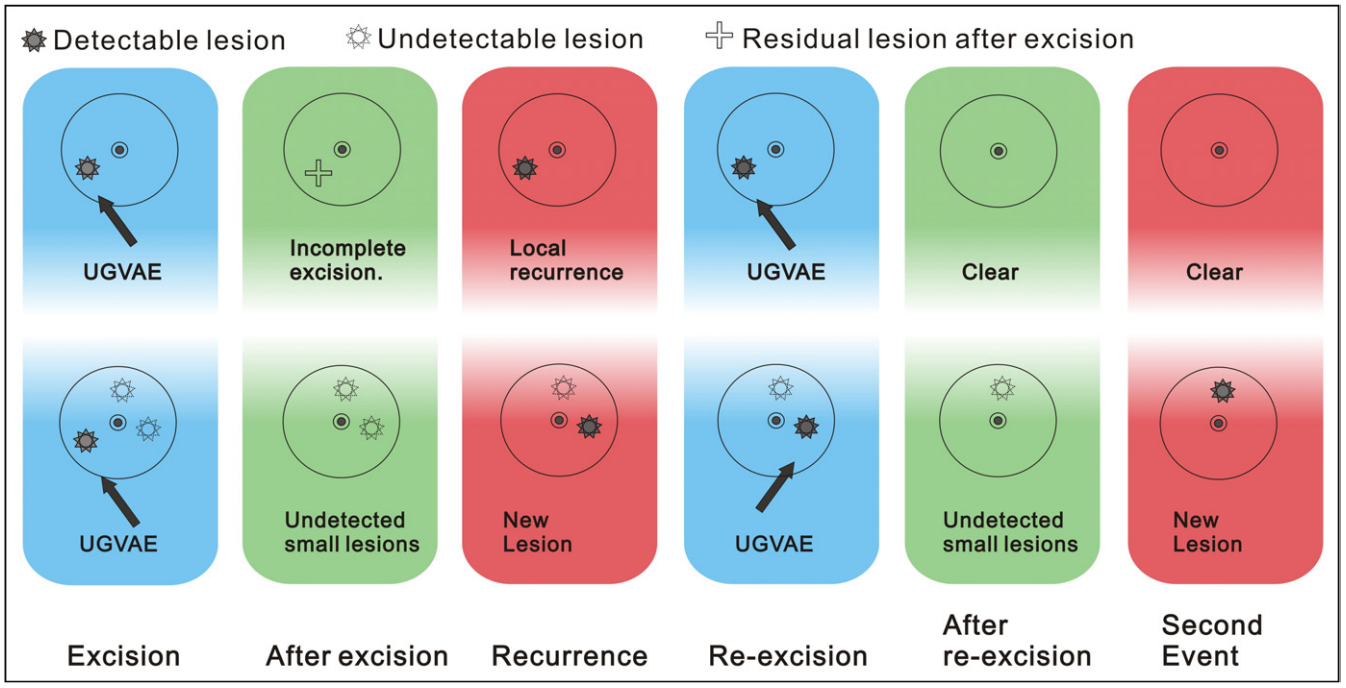


**Figure 1** The hypothesis of the mechanism underlying the different patterns of recurrence. An incomplete excision may lead to local recurrence. Re-excision in these patients is worthwhile to achieve lesion clearance. For patients with new lesions, small lesions that cannot be detected by ultrasound during the initial treatment or the sites that were prone to have abnormal changes may be the cause. Re-excisions might not be worthwhile because second new lesion events may still occur.

Currently, no studies have focused on the pattern of recurrence in patients with benign diseases. In our study, there were 45 and 24 patients with local recurrence and new lesions, respectively. Our data revealed that patients with local recurrences tend to have a larger lesion size and single lesion when compared with patients with new lesions. Larger lesion sizes may increase the chances of leaving residual lesions after UGVAE. Therefore, we proposed that the local recurrence with the same site as that of the original lesions possibly resulted from the regrowth of the retained lesion because of the incomplete excisions. By contrast, patients with new lesions tend to have multiple lesions when compared with patients with in situ recurrence. As discussed previously, the microenvironment and genetics of these patients might be suitable for the development of benign diseases. Herein, we hypothesized that new lesions in a different site than the original lesions were possibly caused by the development of small lesions that could not be detected by ultrasound during the initial diagnosis.

Grady et al[11] suggested that the recurrence was caused by the growth of those small lesions rather than incomplete re-excisions because the ultrasound examinations did not show any residual lesions after the initial excisions. However, they did not make any distinction between local recurrence and new lesions in their study. We would like to argue that the microscopic residual lesions resulting from the incomplete excisions may not always be detected by ultrasound. Thus, local recurrence may still result from an incomplete excision.

In our study, 30 of 45 patients with local recurrence events received re-excisions, and no second recurrence events (0/30) were observed (Table 4). It seemed that re-excision in these patients was worthwhile to achieve lesion clearance because no second recurrence events were observed. On the contrary, in the 24 patients with non–in situ recurrence, 15 of them received re-excisions. Second recurrence events were observed in 5 patients (5/15) after re-excisions. These interesting findings indicated that patients with new lesions are more likely to have additional events after re-excisions. In addition, it should be noted that the 5 patients with a second new lesion event after re-excision had the same pathology subtype of benign disease (fibroadenoma) when compared with their previous ones. Herein, we once again confirm the previous conclusion that the fibroadenoma should be managed with a conservative strategy. Taken together, our data suggested that an incomplete excision may lead to local recurrence, and re-excision was appropriate for these patients to achieve lesion clearance. By contrast, the biological susceptibility may be the reason for the development of new lesions. Considering that more new lesions may still emerge after re-excisions, a conservative strategy such as close surveillance or fine needle biopsy would be the optimal choice (Fig. 1).

The main limitation of our study is that we still lack some important variables. Menopause status, size and dense of the breast, calcifications, radiograph appearance, and duration of the procedure may all have an impact on clinical outcomes. We performed univariate and multivariate anal-

yses on risk factors for recurrence events. We were unable to identify risk factors for local recurrence and new lesions because of the small sample size. Our study is the largest series cases with immediate clinical outcomes; however, a longer follow-up is still needed.

## Conclusions

This is a study with the largest population thus far evaluating the clinical outcomes of patients with breast benign diseases after UGAVE. Univariate and multivariate analysis revealed that lesion number (multiple vs Single), lesion size ($\geq$1 cm vs $<$1 cm), and the presence of a hematoma independently predicted the recurrence events. Our study is the first to suggest that recurrence events could be categorized into local recurrence and new lesions. Patients with local recurrence were more likely to have a large lesion size and more samples taken per lesion, whereas patients with new lesions tended to have multiple lesions at the initial diagnosis. A difference of biological mechanism may exist between local recurrence and new lesions and deserve our clinical attention. Re-excisions may achieve final clearance of benign diseases in patients with local recurrences. In patients with new lesions, second events may still occur even after re-excisions, and close surveillance might be the optimal choice for these patients.

## References

1. Caleffi M, Filho DD, Borghetti K, et al. Cryoablation of benign breast tumors: evolution of technique and technology. Breast 2004;13:397–407.
2. Cole P, Mark EJ, Kaplan SD. Incidence rates and risk factors of benign breast neoplasms. Am J Epidemiol 1978;108:112–20.
3. Bartow SA, Pathak DR, Black WC, et al. Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. Cancer 1987;60:2751–60.
4. Houssami N, Cheung MN, Dixon JM. Fibroadenoma of the breast. Med J Aust 2001;174:185–8.
5. Carter CL, Corle DK, Micozzi MS, et al. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. Am J Epidemiol 1988;128:467–77.
6. London SJ, Connolly JL, Schnitt SJ, et al. A prospective study of benign breast disease and the risk of breast cancer. JAMA 1992;267:941–4.
7. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146–51.
8. Iwuagwu O, Drew P. Vacuum-assisted biopsy device-diagnostic and therapeutic applications in breast surgery. Breast 2004;13:483–7.
9. Bear HD. Image-guided breast biopsy—how, when, and by whom? J Surg Oncol 1998;67:1–5.
10. Zannis VJ, Aliano KM. The evolving practice pattern of the breast surgeon with disappearance of open biopsy for nonpalpable lesions. Am J Surg 1998;176:525–8.
11. Grady I, Gorsuch H, Wilburn-Bailey S. Long-term outcome of benign fibroadenomas treated by ultrasound-guided percutaneous excision. Breast J 2008;14:275–8.
12. Kim MJ, Park BW, Kim SI, et al. Long-term follow-up results for ultrasound-guided vacuum-assisted removal of benign palpable breast mass. Am J Surg 2010;199:1–7.
13. Page DL, Dupont WD, Rogers LW, et al. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer 1985;55:2698–708.
14. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. N Engl J Med 2005;353:229–37.
15. Worsham MJ, Raju U, Lu M, et al. Multiplicity of benign breast lesions is a risk factor for progression to breast cancer. Clin Cancer Res 2007;13:5474–9.
16. Fine RE, Whitworth PW, Kim JA, et al. Low-risk palpable breast masses removed using a vacuum-assisted hand-held device. Am J Surg 2003;186:362–7.
17. Fine RE, Boyd BA, Whitworth PW, et al. Percutaneous removal of benign breast masses using a vacuum-assisted hand-held device with ultrasound guidance. Am J Surg 2002;184:332–6.
18. Zografos GC, Zagouri F, Sergentanis TN, et al. Hematoma after vacuum-assisted breast biopsy: are interleukins predictors? Onkologie 2009;32:395–7.