

Original Article

Effects of high-intensity focused ultrasound combined with neoadjuvant chemotherapy treatment on the biological behaviors of breast cancer

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Abstract: The aim of this study was to evaluate the efficacy of HIFU plus neoadjuvant chemotherapy on breast cancer. 101 patients with biopsy-proven breast cancer were divided into two groups: the group of HIFU plus neoadjuvant chemotherapy (n=50) and group of neoadjuvant chemotherapy (n=51). The therapeutic effect (the tumor volume and the pathological analysis of the tumor mass) was investigated for both groups. The patients in HIFU plus neoadjuvant chemotherapy group had significantly smaller tumor volumes than patients in neoadjuvant chemotherapy group after treatment (18.72 ± 20.38 vs 8.28 ± 9.09 , $P < 0.05$). Pathological analysis indicated that HIFU enhanced the pathological complete response of the neoadjuvant chemotherapy therapy. HIFU is a safe and effective supplementary treatment to neoadjuvant chemotherapy in breast cancer. It is useful in the local therapy of breast cancer.

Keywords: High-intensity focused ultrasound, neoadjuvant chemotherapy, breast cancer

Introduction

Breast cancer is the most common cancer affecting women and accounts for the second highest incidence of cancer-related death, after lung cancer [1]. Breast cancer is treated in several ways. High-intensity focused ultrasound (HIFU) is a highly precise medical procedure used locally to heat and destroy diseased tissue through ablation which is investigated for local treatment of breast cancer and other solid tumors [2, 3]. Neoadjuvant chemotherapy is a well systemic approach of treatment in locally advanced breast cancer which allows breast-conserving surgery in many patients and provides prognostic information that could guide the choice of treatments to maximize the degree of response [4]. How about the treatment effect of combination therapy of HIFU and neoadjuvant chemotherapy in breast cancer therapy? In the present study, we investigated the efficacy of HIFU combined with neoadjuvant chemotherapy treatment on the breast cancer.

Patients and methods

Clinical data

101 patients with biopsy-proven breast cancer in Department of Breast Surgery, the First Affiliated Hospital of China Medical University (China) between Jan 2005 and Feb 2009 were divided into two groups: the group of HIFU plus neoadjuvant chemotherapy (n=50), the group of neoadjuvant chemotherapy (n=51). The average age of the combined therapy group was 44.7 years (range from 28 to 63); the average age was 45.8 years (range from 30 to 59) in the group of neoadjuvant chemotherapy. The sizes of tumor mass were measured by ultrasound. Tumor volumes were calculated using the formula of an ellipsoid [5]. The clinical characteristics of both groups were shown in **Table 1**. The patients in group neoadjuvant chemotherapy were all given adjuvant chemotherapy with cyclophosphamide (C, 600 mg/m²), epirubicin (E, 80 mg/m²), and 5-fluorouracil (F, 600 mg/m²) or docetaxel (T, 75 mg/m²) and cisplatin (P,

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Table 1. Clinical information of the group of combined therapy and the group of neoadjuvant chemotherapy

Characteristics	Neoadjuvant chemotherapy group	Combined therapy group
<i>Age</i>		
<35 years	4	7
≥35 years	47	43
<i>Tumor Volume</i>	29.89±32.97	35.66±37.56
<i>Location of tumor</i>		
<i>Outer quadrant</i>	25	28
<i>Inner quadrant</i>	12	8
<i>Upper quadrant</i>	9	6
<i>Inferior quadrant</i>	1	0
<i>Areola area</i>	4	8
<i>Tumor size</i>		
<2 cm	5	4
2-5 cm	11	13
≥5 cm	35	33

The age and the tumor size between two groups were no significant differences ($P>0.05$).

120 mg/m²). The combination therapy group was all given adjuvant chemotherapy with CEF or TP; it was also given the HIFU treatment. The CJY-HIFU-2005 tumor therapy system was used for HIFU therapy in 10 days after the first neoadjuvant chemotherapy. With the HIFU treatment, the patients were put in supine position. The tumor of breast was divided into sections with 5-mm separation on ultrasound. The scan speed on lateral wall was 3 mm/sec. HIFU energy exposures of 1-3 seconds separated by 2-3 seconds were applied to ablate one target spot. The treatment power was 600 W and the focal length was 150 mm. To avoid thermal damage to adjacent tissues, the focus of HIFU energy beam was kept at least 1 cm away from the tumor margin. All patients follow the modified radical mastectomy or conservative surgery after the treatment. Breast cancer tissue samples were obtained from surgical resection. Pathology classification was based on the WHO's criteria published by Tavassoli et al. [6-8]. Clinicopathological information of each patient was reviewed using the hospital medical records. The study protocol was reviewed and approved by the Ethics Committee of China Medical University (Shenyang, China) and of the participating hospital (the First Affiliated Hospital of China Medical University, Shenyang, China). All patients enrolled in this study have signed an informed consent form to agree to

participate in this study and for publication of the results. There clinical characteristics of patients with breast cancer were shown in **Table 1**.

Evaluation of the therapeutic effect

After the treatment, all patients follow the modified radical mastectomy or conservative surgery. The therapy response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST). Clinical response was categorized into four groups: a complete response (CR) was defined as complete resolution of all tumor determined by physical examination and imaging studies; a partial response (PR) was defined as incomplete reduction >50% in tumor size; a stable disease (SD) was defined as a reduction in tumor size <50%; and progressive disease (PD) was defined as an increase in tumor size. Pathologic size was defined as the greatest dimension of residual invasive tumor and was categorized using the revised American Joint Committee on Cancer TNM staging system [9]. The side reaction of each group was accessed also. Before the treatment of each group and after the treatment, biopsy specimens of the breast cancer were collected from all cases. The sections of each specimen were HE stained and were observed at the magnification of 200×. A high power field with epithelium was randomly selected from each section. The pathological analysis on the surgical resection margins were also performed in all cases.

Statistical analysis

SPSS version 13.0 for Windows was used for all analyses. Data values were expressed as means ± SD. The χ^2 test was used to evaluate the different in response rates between combined therapy and neoadjuvant chemotherapy. The differences in age and tumor size between the two groups were also used the χ^2 test. The differences in tumor volume between the two groups were assessed using the t test. The differences in the reduction of tumor volume before and after the treatment in both groups were assessed using the t test. $P<0.05$ was considered statistically significant. All reported P values are two-sided.

Results

Safety and tolerability

Almost all patients in both groups temporarily suffered obvious side reaction such as nausea, vomiting, mouth soreness, temporary lowering

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Table 2. Response rates of combined therapy and neoadjuvant chemotherapy according to RECIST

Response status	Neoadjuvant chemotherapy group (n=51)	Combined therapy group (n=50)	p-value
ORR	32	46	$\chi^2=12.29$ P<0.01
CR	7	13	
PR	25	33	
SD+PD	19	4	
SD	16	4	
PD	3	0	

ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

of the blood counts and hair loss caused by neoadjuvant chemotherapy. In the combined therapy group, without any significant adverse effect such as skin burns or evidence for mastitis and inflammatory swelling during the 10-day post-treatment observation period. HIFU ablation was well tolerated in all patients.

Efficacy

All patients were found eligible for modified radical mastectomy or conservative surgery after the treatment. The therapy response of 101 patients was evaluable. As shown in **Table 2**, ORR in the neoadjuvant chemotherapy group was 32/51 (64.7%), and ORR was 46/50 (92%) in the combined therapy group. The objective response rate was higher in HIFU plus neoadjuvant chemotherapy group than in neoadjuvant chemotherapy group (92.0% vs 64.7%, P<0.05). Our results indicated that the treatment of HIFU plus neoadjuvant chemotherapy can reduce the tumor volume of breast cancer significantly (35.66 ± 37.56 vs 18.72 ± 20.38 , P<0.05) (**Figures 1 and 2**), neoadjuvant chemotherapy can reduce the tumor volume significantly also (29.89 ± 32.97 vs 8.28 ± 9.09 , P<0.05) (**Figures 3 and 4**). The tumor volume after the treatment of HIFU and neoadjuvant chemotherapy was lower than it after the treatment of neoadjuvant chemotherapy (18.72 ± 20.38 vs 8.28 ± 9.09 , P<0.05). There is more information on the treated nodules (**Table 2**).

Pathological analysis

Our data indicated that a total of 7 (13.7%) patients had clinical complete response (cCR) in the neoadjuvant chemotherapy group. It is interesting to note that of these 7 patients, only 3 patients (5.8%) had a correlating pathological complete response (pCR; **Figures 5 and 6**). Of

the 13 patients with pCR (26.0%) in the combined therapy group, only 7 (14.0%) had correlating cCR. HIFU enhanced the pathological complete response of the neoadjuvant chemotherapy therapy.

Discussion

The HIFU therapy utilizes mechanical energy in the form of a powerful ultrasound wave which is focused inside the body to induce thermal and/or mechanical effects in tissue. Consequently, HIFU requires less anesthetic, makes infection highly unlikely and precludes scar formation. As such, patient acceptance of HIFU is high [10]. It is an alternative ablative technique for local treatment of breast cancer and other solid tumors. HIFU's main shortcomings observed during treatment are related to its local treatment. So it is not a general treatment, it is not effective to the micrometastases of cancer. Neoadjuvant chemotherapy refers to the systemic treatment of breast cancer prior to definitive surgical therapy which offers the possibility to treat both primary lesions and micrometastases at distant sites. So we combined the HIFU and neoadjuvant chemotherapy. If the combined therapy is clinically proven to be an effective modality for the treatment of breast cancer by a well-designed study, it can be used in conjunction with the current treatment schemes to improve the therapy efficacy. In the present study, HIFU ablation was performed successfully in all patients of combined therapy group. It was well tolerated and no local complication occurred. Previous reported the HIFU is a completely noninvasive ablation technique which focused beams of ultrasound are used for ablation of the target lesion without disrupting the skin and subcutaneous tissues in the beam path [11]. The results from early clinical trials (Phase I and II) are encouraging which suggested that HIFU is a promising treatment for small breast cancer without systemic complications [12]. Compared with the neoadjuvant therapy group, the combination therapy of HIFU and neoadjuvant chemotherapy had higher response rates, higher clinical complete response rates, and higher pathological complete response rate. The tumor volume after the treatment of combined therapy was lower than it after neoadjuvant chemotherapy.

Although the noninvasive ablation technique of HIFU has received increasingly widespread

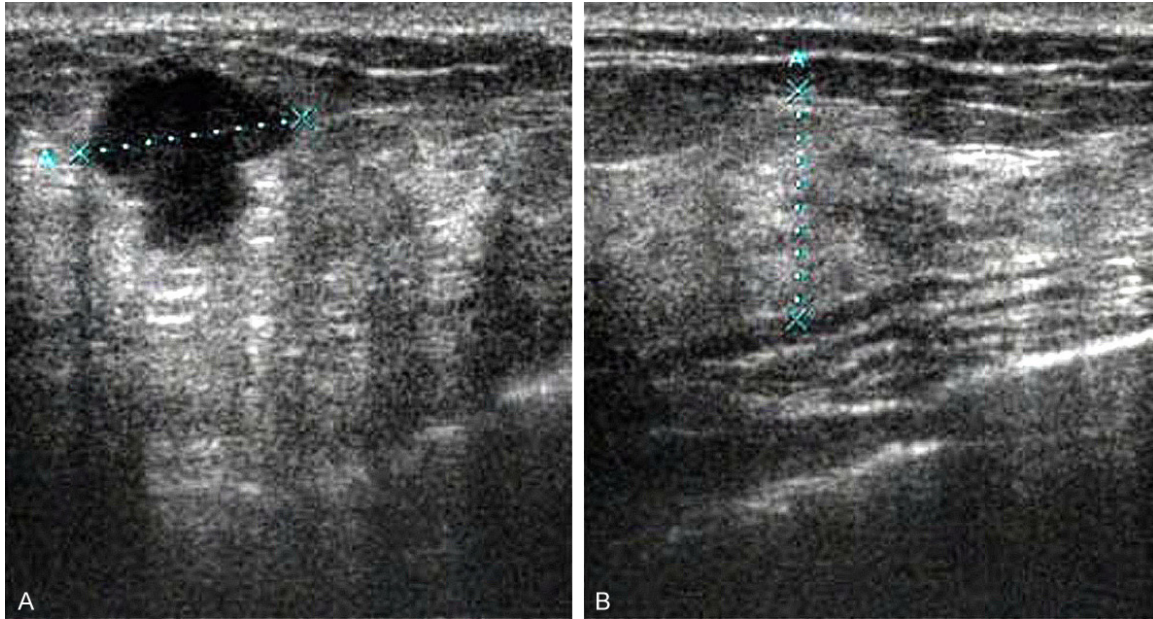


Figure 1. Volume measurement. Sonographical volume measurement of the breast cancer mass before (A) and after (B) HIFU plus neoadjuvant chemotherapy treatment.

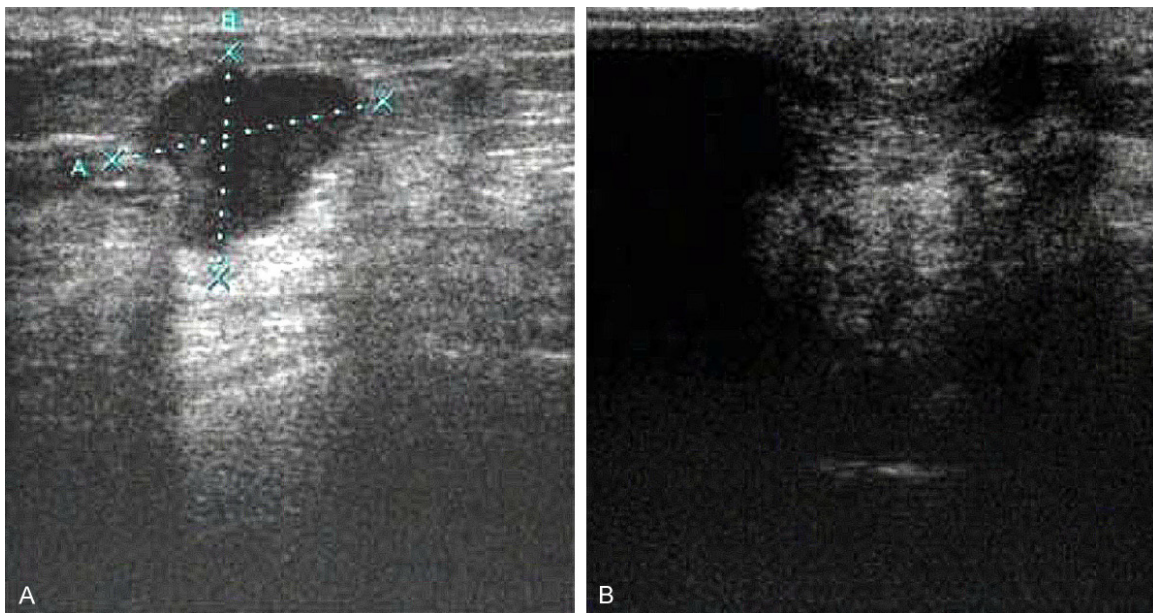


Figure 2. Volume measurement. Sonographical volume measurement of the breast cancer mass before (A) and after (B) HIFU plus neoadjuvant chemotherapy treatment.

interest, the first step and most common form of treatment for breast cancer is surgery in our viewpoints. The neoadjuvant chemotherapy treatment for breast cancer was preserved for locally advanced breast cancer, converting an inoperable to a surgical resectable cancer [13]. In recent years, neoadjuvant therapy has become an accepted treatment option also for

shrink the cancer in order to increase the rate of breast conserving therapy and to reduce the extent of surgery. Neoadjuvant chemotherapy was systemic, it use substances that travel through the bloodstream, reaching and affecting cancer cells all over the body. Our results indicated that the HIFU therapy was a local supplementary treatment with neoadjuvant ch-

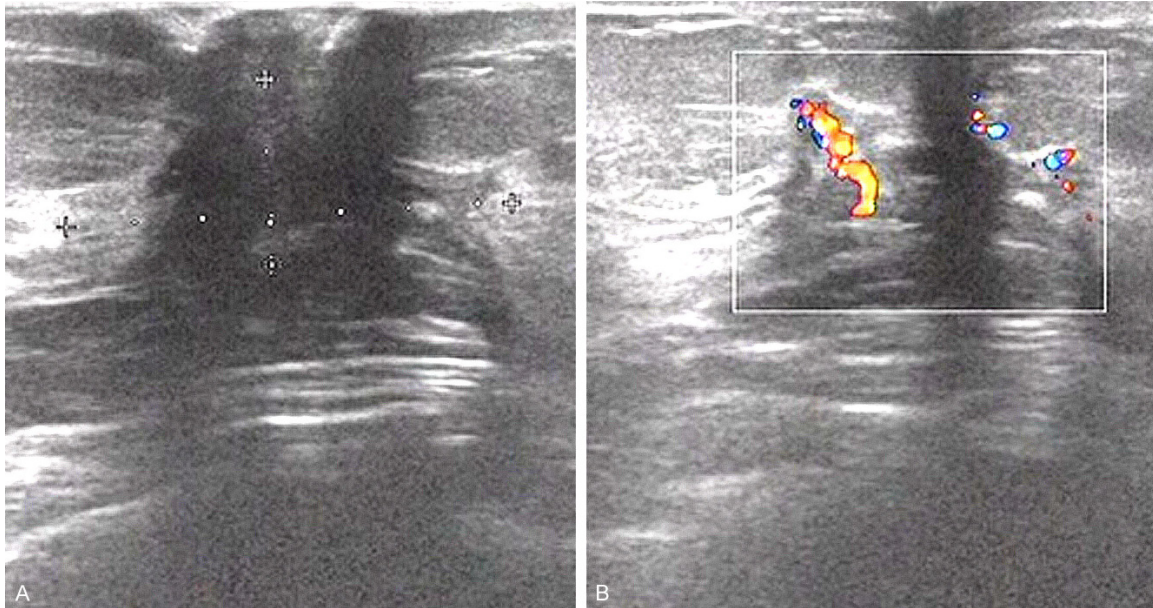


Figure 3. Volume measurement. Sonographical volume measurement of the breast cancer mass before (A) and after (B) neoadjuvant chemotherapy treatment.

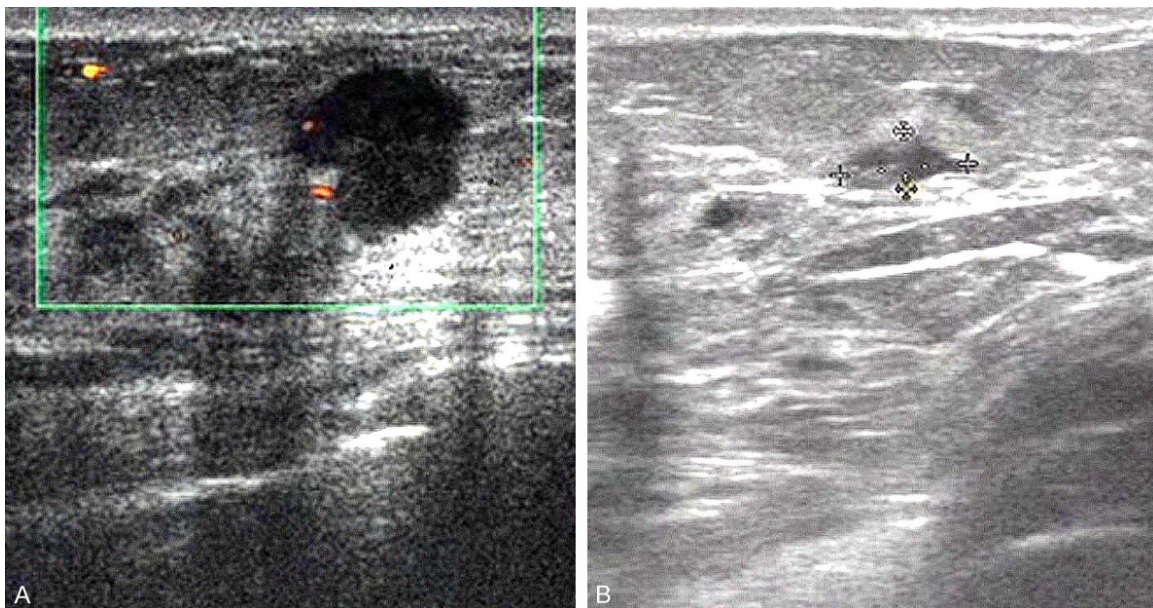


Figure 4. Volume measurement. Sonographical volume measurement of the breast cancer mass before (A) and after (B) neoadjuvant chemotherapy treatment.

emotherapy to shrink breast cancer. HIFU requires no insertion of applicators, and it is non-invasive. And the procedure can be easily repeated and large ablation areas can be induced under imaging guidance in one treatment session. It is a hyperthermia therapy, a class of clinical therapies that use temperature to treat breast cancer. It is only useful to treat a single tumor or part of a large tumor; it is not the key

therapy for the widespread breast cancer. HIFU doesn't pass through either solid bone or air. It was a useful supplementary treatment to neoadjuvant chemotherapy in breast cancer. It enhanced the local treatment effect of neoadjuvant chemotherapy to shrink the tumor. It was well tolerated without local complication. We always support the viewpoint that it can't replace the surgery on the breast cancer treat-

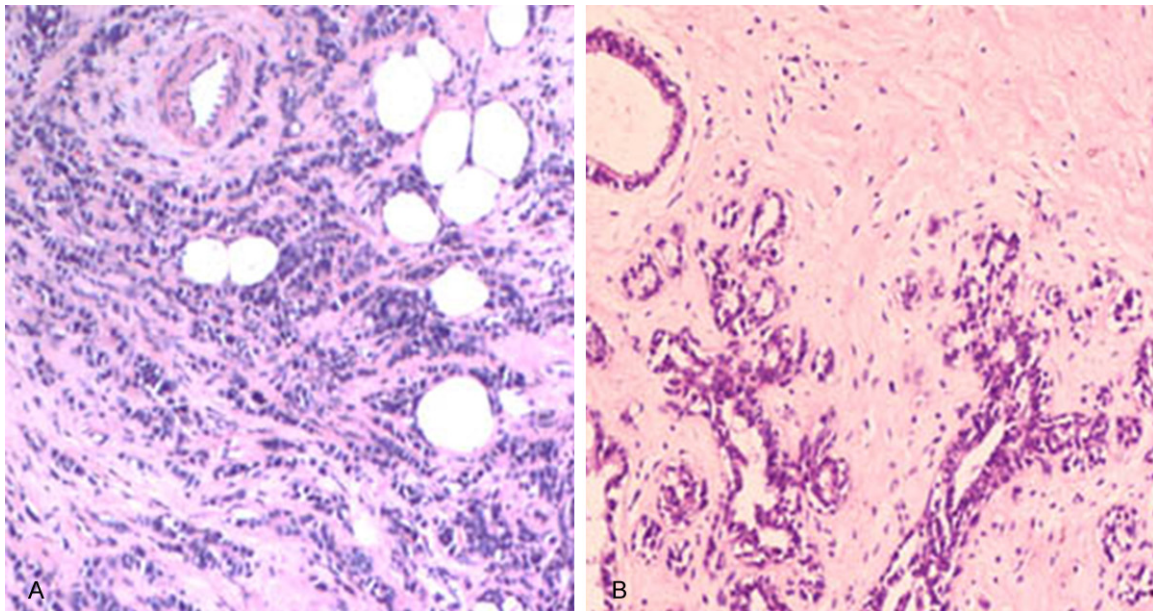


Figure 5. Pathological changes of breast carcinoma. The pathology of a breast cancer case before (A) and after (B) HIFU plus neoadjuvant chemotherapy treatment.

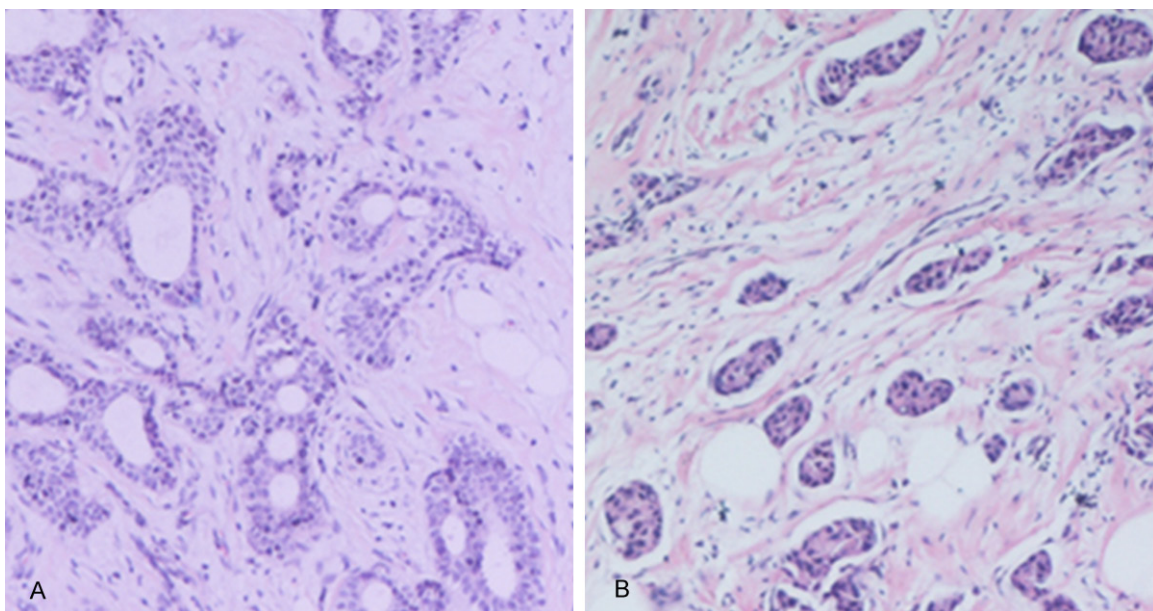


Figure 6. Pathological changes of breast carcinoma. The pathology of a breast cancer case before (A) and after (B) neoadjuvant chemotherapy treatment.

ment with the current research data. HIFU plus neoadjuvant chemotherapy improved the efficacy of breast cancer treatment.

In summary, the results of this study suggest that HIFU is a safe and effective supplementary treatment to neoadjuvant chemotherapy in breast cancer. It is useful in the local therapy.

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Disclosure of conflict of interest

None.

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