

Clinical Observation and Retrospective Analysis of the Effect of Comprehensive Treatment on Hepatic Hemangiomas in HR Positive Breast Cancer Patients

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Research article

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Abstract

Objective: To retrospectively assess the size change of hepatic hemangiomas (HH) in hormone receptor positive (HR+) breast cancer patients after comprehensive treatment.

Methods: Totally 364 confirmed invasive breast cancer cases with HH were diagnosed at the Breast Cancer Center of Yunnan Cancer Hospital in 2013-2018 by abdominal color Doppler ultrasound (ADUS) + contrast enhanced ultrasound (CEUS) and at least one upper abdominal CT imaging examination. Follow-up was 6-78 months, and changes in location, number and size of HH at different treatment stages were compared between the HR+ and 85 HR- groups. Subgroup analysis of patients receiving chemotherapy and endocrine therapy was also performed.

Results: Totally 323 patients were enrolled, including 238 HR+ (73.7%) and 85 HR- (26.3%) cases. Changes in the longest diameter were similar in both groups ($P=0.556$), and size change of HH was not associated with axillary lymph node metastasis of breast cancer ($P>0.05$). HH showed no change during chemotherapy but was significantly enlarged after chemotherapy ($P<0.01$). There was no significant difference between the tamoxifen (TAM; endocrine drug) only and combination or sequential endocrine treatment ($P>0.05$) groups. Only the aromatase inhibitor group showed statistical significance ($P<0.05$) in the AI (letrozole, anastrozole and exemestane) group at the t1 time point.

Conclusion: During chemotherapy and endocrine therapy for breast cancer patients with HH, the size of HH changes in some patients, while others develop new HH. No significant effect on size change of HH was observed in this study.

Introduction

Hepatic hemangiomas (HH) are common benign vascular endothelial tumors of the liver^[1], with a higher incidence in women compared with men. They are more common in infants, and less frequent in adults^[2]. HH do not cause apparent symptoms commonly, and are incidentally detected during clinical examination for other diseases^[3]. The pathogenesis of HH remains unclear, and multiple studies have focused on surgical treatment^[4,5]. It was pointed out that the effect of estrogen is closely associated with the growth of HH^[6]. Currently, there are no clinical observation data describing the effect of estrogen-inhibiting therapy on HH. Endocrine therapy is the standard maintenance treatment option for hormone receptor positive (HR+) breast cancer patients^[7]. HR+ breast cancer cases with HH show substantial changes in HH under different treatments after systematic anti-tumor therapy. In this study, the notion of size change in HH by breast cancer-related treatment was confirmed in a retrospective study, and clinical data on the effect of endocrine therapy on HH are firstly provided [Chinese Clinical Trial Registry 2000033089].

Patients And Methods

1.1 Data collection

Totally 364 cases of confirmed breast cancer patients with HH at Yunnan Cancer Hospital from January 1, 2013 to December 31, 2018 were enrolled, and 323 cases were finally assessed. Among them, 238 cases (73.7%) were HR+, and 85 (26.3%) were HR-. This retrospective clinical study was approved by the Ethics Committee of the above hospital, and did not require written informed consent.

1.2 Basic patient characteristics

the size change of HH in various patients during the treatment were recorded. Since HH are non-solid tumors, the RECIST efficacy evaluation standard [8] for solid tumors is not fully applicable for statistical analysis. Therefore, the longest diameter and (long diameter × short diameter) of the HH were adopted for statistics. Diagnosis of HH mainly depends on imaging examination, without the need for puncture biopsy. The final inclusion criteria were: (1) age ≥ 18 years and ≤ 80 years; (2) female patients pathologically diagnosed with invasive breast cancer and HH by abdominal ultrasound + contrast enhanced ultrasound + upper abdominal CT [4][9]; (3) single or multiple HH found by imaging evaluation; (4) good liver function, Child-Pugh grade A; (5) generally good patient condition and cardio-pulmonary function that can tolerate operation. Exclusion criteria were: (1) incomplete follow-up data; (2) a history of upper abdominal operation; (3) previous effective treatment for HH; (4) combined with hepatic malignant tumors. Relevant indicators such as gallbladder disease, fatty liver, hepatic cyst, intrahepatic calcification, chemotherapy regimen and frequency were recorded accordingly after enrolment. the size change of HH in all cases during the follow-up period was evaluated by abdominal Doppler ultrasound, and examination reports were provided by different sonographers with intermediate qualifications or above in the Ultrasound department. All data were sent to Shanghai MedSci for statistical analysis.

1.3 Statistical analysis

data were statistically analyzed by SPSS 22.0 and GraphPad Prism 6. Normally distributed quantitative parameters are mean \pm SD, and were compared by independent samples t-test. Median (IQR) was used for continuous variables with skewed distribution, which were assessed by the Mann-Whitney U test. Qualitative variables were described by N (%), and compared by the chi-square test or Fisher exact probability test. Overall comparisons of the longest diameter, long diameter × short diameter, longest diameter difference and long diameter × short diameter difference were performed using a generalized estimating equation. The Mann-Whitney U test was performed to compare various time points from t1 to t14 between the two groups, and the Kruskal-Wallis test was carried out among-group comparisons. The Wilcoxon test was performed for comparing t14 and t1. Two-sided P<0.05 was considered statistically significant.

Results

2.1 Baseline patient information

Totally 323 cases of breast cancer with HH were enrolled (table 1). Among them, 238 cases were HR+, with a median age of 46.07±8.08 years, and 85 were HR-, with a median age of 46.73±8.16 years. TNM staging of breast cancer was performed, and most cases were stage II. There were 130 stage II cases (54.62%) in the HR+ group, and 44 (51.76%) in the HR- group (P=0.419). A total of 125 patients (52.52%) had lymph node metastasis in the HR+ group, versus 47 (55.29%) in the HR- group (P=0.660). HH generally presented as single lesions, including 193 (81.09%) and 67 (78.82%) cases in the HR+ and hr-groups, respectively (P=0.650). They were mostly found in the right lobe of the liver (71.85%) versus 27.73% in the left lobe. There were 171 (71.85%) and 57 (67.06%) cases of HH in the right lobe of the liver in the HR+ and hr- groups, respectively (P=0.650). The selection of the chemotherapy regimen for breast cancer was mainly based on the NCCN guidelines. The most commonly used chemotherapy regimen was epirubicin plus cyclophosphamide with sequential paclitaxel, which was administered in 164 patients (68.91%) of the HR+ group, versus 50 (58.82%) in the hr- group (P=0.531). The initial time of HH diagnosis was before and during chemotherapy in 207 (86.97%) cases of the HR+ group, versus 74 (87.06%) in the HR- group. There were 17 cases (7.14%) of HH in the HR+ group diagnosed after chemotherapy, versus 8 (9.14%) in the HR- group (P=0.584). The enrolled patients were followed up by outpatient review or via the hospital's medical records until July 1, 2019, at a follow-up frequency of 3 months. The drugs used for endocrine therapy in the HR+ group included tamoxifen, AI (letrozole, anastrozole, and exemestane), fulvestrant and ovarian function inhibitors. Endocrine therapy for breast cancer was based on NCCN guidelines for drug selection. A total of 127 patients (53.36%) were treated with tamoxifen only, 86 (36.13%) were administered AI only, and other treatments were used in 25 patients (10.5%).

2.2 Size change of HH at different time points

Of all the enrolled cases, 221 (65.3%) of HH were found before systematic treatment. During the treatment of breast cancer, a total of 84 patients (26%) had HH during chemotherapy. In addition, less patients developed HH during endocrine drug therapy after a comprehensive treatment of breast cancer, accounting for 28 cases (8.7%). The enrolled breast cancer patients with HH were divided into the experimental (HR+) and control (hr-) groups, and size changes of HH at 14 treatment time points (t1-t14) were analyzed, as shown in table 2. The time of initial diagnosis of HH was considered the first time point (t1), and the time of each detection of HH sequentially corresponded to the respective time point until t14. In some patients, the absence of ultrasound and CT examinations may lead to data loss. The t1 time point was used as the baseline, and cases with no missing data for HH at t1 were included in the analysis. The time points from t1 to t8 comprised the stages of chemotherapy and surgery, with an interval of 21 days. The time points from t9 to t14 encompassed the period of endocrine therapy, with an interval of 6 months.

As shown in Figure 1A and B, HH in the experimental group showed a decreasing trend in size after comprehensive breast cancer treatment, while that of the control group showed no overall decreasing trend. All P values were greater than 0.05, indicating no statistical significance.

2.3 Size changes of HH at different time points

The sizes of HH in the experimental group varied at different treatment time points (Figure 2A and 2B). As shown in Figure 2A, size (longest diameter) changes of HH between the experimental and control groups had no obvious differences ($P>0.05$). In Figure 2B, a significant difference was obtained at t12 in size change for HH between the experimental and control groups, when the long diameter \times short diameter was considered ($P=0.049$). However, the other time points showed no statistically significant differences between the two groups.

2.4 Relationship between axillary lymph node metastasis and size change of HH

In breast cancer patients with or without axillary lymph node metastasis, once the diagnosis is confirmed, there are certain differences in the selection of therapeutic schedules. In those with axillary lymph node metastasis, chemotherapy regimens and cycle time are more intensive and longer, respectively, compared with those of cases without axillary lymph node metastasis; in addition, the selection of chemotherapy drugs and subsequent endocrine drugs also shows differences. As shown in Figure 3, in both the experimental and control groups, the sizes of HH showed a decreasing trend after the comprehensive treatment of breast cancer at the later time point of t10. However, whether or not axillary lymph node metastasis was present, the longest diameter (Figure 3A, 3B) and (long diameter \times short diameter) (Figure 3B, 3D) showed no significant differences between the experimental and control groups.

2.5 relationship between occurrence time and the size change of HH

Most breast cancer patients require chemotherapy because of the invasiveness of breast malignant tumors. according to different occurrence time points of HH in confirmed breast cancer patients administered chemotherapy, the enrolled cases were divided into two groups, with occurrence before or during and after chemotherapy, respectively. Therefore, the patients with HH detected before the initial treatment of breast cancer and those with new HH during chemotherapy were assigned to the “during chemotherapy” group, and cases still with HH and those with new HH after chemotherapy constituted the “after chemotherapy” group. Both groups were compared in Figure 4.

The results showed that HH did not decrease in size significantly during chemotherapy, but also had no increasing trend, tending to be stable. Based on long diameter, the HH were significantly smaller after chemotherapy than during chemotherapy, and the difference between the two groups was significant ($P<0.001$; Figure 4A and C). In Figure 4B and D, the difference in the size change of HH based on long diameter \times short diameter was significantly larger after chemotherapy than during chemotherapy.

2.6 Relationship between endocrine therapy and the size of HH

Endocrine drug treatment is used for subsequent maintenance therapy in HR+ breast cancer patients, with tamoxifen and AI as the first-line drugs ^[10]. Patient data obtained by follow-up were grouped for statistical analysis. Patients treated with tamoxifen only were assigned to one group; those administered

AI only were assigned to another group, and cases treated with combined or sequential use of other endocrine drugs (including tamoxifen + ovarian function inhibitors, tamoxifen sequential AI, fulvestrant, *etc.*) formed the third group. The experimental results are shown in Figure 5. Compared with the other two groups, patients treated with AI endocrine drugs at t10 showed a statistically significant difference ($P < 0.05$; Figure 5A). The other endocrine drugs at t10 and t11 also showed statistically significant differences ($P < 0.05$), but there were no differences between the whole group and the other two groups (figure 5C). There were no differences among groups based on long diameter \times short diameter (Figure 5B and D).

2.7 changes in various groups between t14 and t1

HR positivity, axillary lymph node metastasis, hemangioma occurrence before or after chemotherapy, and the effects of different endocrine drugs on the size of HH at t14 and t1 (Table 3) showed no differences in the “other” group. There was a significant difference in hemangioma size determined as longest diameter between patients treated with AI endocrine drugs and the other two groups, while the tamoxifen group showed no difference compared to the other two groups.

Conclusion

In breast cancer patients with HH, no significant reduction of HH was observed in the HR+ experimental and HR- control groups, and there were no differences between the two groups at various time points. The size differences between HH in the experimental and control groups at different time points and the relationship between hemangioma occurrence time and chemotherapy were evaluated. The size change of HH at various time points in the HR+ group showed a downward trend, and the difference in size change during chemotherapy was smaller than that after chemotherapy. Chemotherapy drugs may have a certain vasoconstrictor effect on HH in breast cancer patients, thus limiting tumor growth. There was no significant increase in HH during chemotherapy between the two groups, and the difference in size change of HH gradually increased after chemotherapy. breast cancer patients with HH, with axillary lymph node metastasis or not, have similar size changes of HH after the comprehensive treatment. In patients treated with AI endocrine drugs, HH, as calculated by the longest diameter or long diameter \times short diameter, showed reduced growth. Similar results were obtained for t14 versus t1. In the endocrine therapy, there were significant differences between the AI endocrine drugs and other groups. In conclusion, the slow growth of HH during chemotherapy demonstrated that AI endocrine drugs inhibit HH, which is not the case for tamoxifen.

Discussion

With the development of medical technology and the increasing number of breast cancer patients year by year, diagnosed breast cancer cases with HH are also more common in clinical practice. Although HH are common benign tumors, small ones generally have limited effects on the daily life and health^[1], and regular follow-up is enough^[11]. However, when HH are larger than 5 cm, termed giant HH^[12], abdominal

masses, hemangioma rupture and hemorrhage could occur, as well as related clinical symptoms ^{[13][14]}. Symptomatic HH and giant HH have therapeutic indications ^{[12][15]}.

The exact pathogenesis of HH is currently unclear, and related theories suggest that it involves the congenital malformation of blood vessels, which may also be caused by the stimulation of hormones such as estrogen and progesterone ^[16]. Glannitrapani *et al*^[7] proposed that estrogen is associated with the stimulation of hepatocyte proliferation and could be used as a liver tumor inducer. Breast cancer is a hormone-dependent malignant tumor, and estrone and estradiol are directly related to its incidence ^[17]. It was mentioned in previous studies ^{[7][18]} that female sex hormones may play an important role in the growth of HH. The effect evaluation of female sex hormones on the natural history of HH by E Wolfson Medical Center ^{[19][20]} and a case report on changes of HH by sexual hormones in two postmenopausal women published by The Tohoku Journal of Experimental Medicine in 2006 ^[21], both confirmed that estrogen plays a key role in promoting the development and growth of HH. Among the enrolled cases, there were 238 HR+ (73.7%) and 85 HR- (26.3%) breast cancer patients with HH. HR+ cases were 2.8 times more than HR- counterparts, and the incidence of HH was significantly higher in the former group. Totally 221 breast cancer patients (65.3%) were diagnosed before systematic treatment with HH; 84 patients (26%) developed HH during chemotherapy, and 28 (8.7%) developed HH during endocrine therapy. breast cancer patients not receiving antiestrogen therapy before systematic treatment had the highest proportion of HH. The above data further confirmed that the occurrence of HH in breast cancer patients may be influenced by estrogen stimulation.

Nisreen El-Hashemite *et al*^[22] found that mice with nodular sclerosis Tsc1+/ and Tsc2+/ are prone to develop HH. Mouse liver hemangiomas are composed mainly of endothelial cells, and express estrogen receptor α (ER α) and progesterone receptor (PR). Fang Hou *et al*^[23] also conducted relevant experimental detection of estrogen receptor expression in HH tissues from infants. The results showed that all the HH specimens assessed were ER α positive and ER β negative. ER α is found only in the cytoplasm and nucleus of monocytes, and not expressed in endothelial cells. Estrogen receptor expression was found in both HH endothelial cells and smooth muscle cells in Tsc1+/ mice ^[24], and estrogen enhanced while tamoxifen reduced the frequency and severity of HH. ER α and estradiol are not present in HH endothelial cells from infants. In this study, tamoxifen therapy had no significant effect on the size of HH in breast cancer patients, which suggested that the effectiveness of tamoxifen may be related to the presence or absence of estradiol and estrogen receptor in HH endothelial cells. In endocrine therapy for breast cancer, tamoxifen is structurally similar to estrogen, and can compete with estradiol for estrogen receptors, with which it forms a stable complex. Estrogen receptors include nuclear and membrane receptors; nuclear receptors include ER α and ER β . In case of no estrogen receptor expression in the endothelium of HH, or differential expression of ER α and ER β , tamoxifen therapy may be ineffective. In addition, estradiol levels are different at the three stages of HH growth in infants (proliferation, early degeneration, and late degeneration); therefore, hormone levels and hormone receptor expression may also be affected during the treatment of HH in adults. With increasing age, estradiol levels also differ compared with those observed during the growth of HH in infants. Due to these possible factors, tamoxifen may also differ in

its ability to compete with estradiol for estrogen receptors, affecting the efficacy of tamoxifen in HH treatment.

However, the efficacy of tamoxifen in the treatment of HH cannot be completely overlooked. Estrogen promotes angiogenesis *in vitro* and *in vivo* [25]. In a model of estrogen-dependent breast cancer, estrogen treatment increases the level of vascular endothelial growth factor (VEGF) secreted by tumor cells [26], while tamoxifen reduces these levels [27][28]. Schnaper *et al* [25] reported that tamoxifen, as an anti-angiogenic agent, increases the ratio of vascular endothelial growth factor receptor (VEGFR) 1 to VEGF in endothelial cells, thereby playing a role of anti-angiogenesis [29]. Jinnin *et al* [30] showed that VEGFR1 and VEGFR 2 both bind to vegf, and VEGFR1 negatively regulates VEGFR 2 signaling. In the endocrine therapy stage of breast cancer with HH, tamoxifen may also reduce HH by decreasing VEGF levels and promote anti-angiogenesis. In this study, 127 patients (53.36%) received tamoxifen only. Although no reduction in HH size was observed after tamoxifen treatment, no increase occurred. In case tamoxifen therapy is affected by the absence of related estrogen receptor in the HH endothelium or the expression of different estrogen receptor subtypes, the anti-angiogenic effect of tamoxifen could still reduce or maintain the non-growth state of HH in patients.

Chemotherapy may exert similar inhibitory effects on the growth of HH. In 2012, Vishal Sondhi *et al* [31] reported a case of infant HH cured by tamoxifen plus cyclophosphamide regimen in BMJ. Besides tamoxifen, the patient was treated with the chemotherapeutic drug cyclophosphamide. In this case, the role of cyclophosphamide in the treatment of HH was primarily related to anti-angiogenesis with hypoxia induction [32][33]. Cyclophosphamide is one of the most effective chemotherapeutic drugs in breast cancer, and anthracycline with cyclophosphamide is the usual regimen. In the current study, 164 patients (68.91%) in the HR+ group and 50 (58.82%) in the HR- group received anthracycline + cyclophosphamide with sequential paclitaxel chemotherapy regimen. Anthracycline inhibits division in rapidly growing cancer cells by suppressing DNA replication and RNA synthesis. paclitaxel plays an anticancer role by stabilizing microtubules and inhibiting mitosis in cancer cells as well as inducing cell apoptosis, thus effectively preventing the proliferation of cancer cells. These two chemotherapeutic drugs play an absolute role in the treatment of solid tumors, but have not been currently applied for HH. In subgroup analysis, there were no statistically significant differences between groups in breast cancer patients administered this treatment regimen. Between patients with HH diagnosed during and after overall chemotherapy, it was found that chemotherapy had no effect on the size change of HH. However, the sizes of HH did not increase significantly during chemotherapy, and all cases tended to be stable. This may be due to the anti-angiogenic effect of chemotherapeutic drugs, which prevented the overall size of HH from increasing during chemotherapy, but could not inhibit them. Whether chemotherapeutic drugs can inhibit the growth of HH remains unknown.

The final results showed that AI drugs impact the size of HH. AI drugs can specifically cause aromatase inactivation, block the generation of peripheral estrogen, and reduce estrogen levels in the blood to achieve the purpose of breast cancer treatment. Their mechanism of action does not involve competition

with estradiol for estrogen receptor. Therefore, they can directly reduce estrogen levels, decrease the inducing effect of estrogen on liver hemangioma growth, and inhibit liver hemangiomas. On the other hand, the breast cancer patients treated with AI endocrine drugs were postmenopausal women. Estrogen in postmenopausal women mainly originates from tissues beside ovaries, and shows lower amounts than found in premenopausal women ^[34], which also reduces the inducing effect on HH. Therefore, AI endocrine drugs may be effective for HH in postmenopausal women.

This was a retrospective, single-center study, and data analysis had some limitations. In the process of data collection, statistics was not consistent among various years due to the different diagnostic experiences of sonographers. Due to the long-term side effects of endocrine therapy in breast cancer, patient compliance is reduced, leading to loss to follow-up for some patients. In addition, some patients were still in the stage of endocrine therapy. These limitations will be addressed in future prospective randomized controlled studies. However, the above results are still the first real-life observation of HH after systematic treatment of breast cancer.

In conclusion, endocrine therapy of breast cancer has provided an option for the treatment of HH, although its exact effect still needs further exploration.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Linyan Tan: Conceptualization, Methodology, Software, Writing-Original Draft. **Manting Hu:** Data curation, Writing-Original draft, Conceptualization. **Wenjing Sun:** Writing-Original draft, Investigation, Formal analysis. **Saijun Huang:** Resources. **Yue Tian:** Software, Validation. **Younan Ye** and **Na Li:** Data Curation , Project administration. **Yang Liu:** Investigation. **Dequan Liu:** Resources, Writing- Reviewing and Editing. **Chenxi Yan** and **YinHua Nian:** Software, Formal analysis. **Xi Wang:** Project administration. **Yiyong Duan:** Writing- Reviewing and Editing. **Wenlin Chen** and **Fei Ge:** Writing - Review & Editing, Supervision, Funding acquisition.

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Tables

Table 1

Baseline patient information

variable	HR(+) breast cancer with hepatic hemangioma N=238	HR(-) breast cancer with hepatic hemangioma N=85	P
Age (y)			0.567
Mean±SD	46.07±8.08	46.73±8.16	
Median (IQR)	45 (40,52)	46 (40,53)	
Stage, n (%)			0.419
I	39 (16.39%)	14 (16.47%)	
II	130 (54.62%)	44 (51.76%)	
III	43 (18.07%)	15 (17.65%)	
IV	9 (3.78%)	1 (1.18%)	
Unavailable data from other hospitals	17 (7.14%)	11 (12.94%)	
Position, n (%)			0.456
L	66 (27.73%)	27 (31.76%)	
R	171 (71.85%)	57 (67.06%)	
Fatty liver	91 (38.24%)	34 (40%)	0.774
hepatic cyst	38 (15.97%)	7 (8.24%)	0.077
Intrahepatic calcification	45 (18.91%)	10 (11.76%)	0.133
Combined with gallbladder disease	25 (10.5%)	13 (15.29%)	0.239
hepatic hemangioma			0.650
Single lesion	193 (81.09%)	67 (78.82%)	
Multiple lesions	45 (18.91%)	18 (21.18%)	
chemotherapy regimens			0.531
EC-T	164 (68.91%)	50 (58.82%)	
TC	17 (7.14%)	8 (9.41%)	
TE	28 (11.76%)	11 (12.94%)	
5F-EC	12 (5.04%)	8 (9.41%)	
TEC	13 (5.46%)	6 (7.06%)	

CEF-PTX	3 (1.26%)	2 (2.35%)	
Lymph node metastasis of breast cancer	125 (52.52%)	47 (55.29%)	0.660
occurrence time of hepatic hemangioma			0.584
During the chemotherapy	207 (86.97%)	74 (87.06%)	
After the chemotherapy	17 (7.14%)	8 (9.41%)	
medication regimen			/
Tamoxifen only	127 (53.36%)	/	
Aromatase inhibitor only	86 (36.13%)	/	
Other treatments	25 (10.5%)	/	

Table 2

Sizes of hepatic hemangiomas at different time points

time points	longest diameter		Long diameter × short diameter (mm ²)	
	HR (+) breast cancer with hepatic hemangioma N=238	HR(-) breast cancer with hepatic hemangioma N=85	HR (+) breast cancer with hepatic hemangioma N=238	HR(-) breast cancer with hepatic hemangioma N=85
1				
Mean±SD	9.92±10.74	10.26±12.61	164.45±327.57	208.01±473.54
Median (IQR)	9 (0,15)	9 (0,17)	63 (0,182)	62 (0,221)
2				
Mean±SD	11.41±12.24	9.65±11.18	220.26±594.06	170.96±416.65
Median (IQR)	10 (0,15)	9 (0,15)	80 (0,182)	63 (0,180)
3				
Mean±SD	12.2±10.82	11.99±11.41	202.62±328.3	209.55±418.82
Median (IQR)	11 (0,16)	11 (0,16)	93 (0,209)	99 (0,208)
4				
Mean±SD	12.48±10.95	11.96±11.51	208.49±329.04	220.91±442.12
Median (IQR)	10 (6,17)	10 (0,18)	88 (30,225)	72 (0,228)
5				
Mean±SD	12.8±10.6	12.69±11.39	208±317.45	229.3±438.86
Median (IQR)	11 (7,18)	11 (7,17)	90 (42,238)	99.5 (35,238)
6				
Mean±SD	12.36±10.07	12.59±10.95	193.08±291.95	222.44±425.08
Median (IQR)	11 (7,17)	11 (6,18)	90 (37.5,224)	98 (30,228)
7				
Mean±SD	13.14±10.23	12.96±11.22	208.48±319.8	221.45±422.89
Median	11 (8,17)	12 (7,18)	99 (45,204)	99 (35,240)

(IQR)				
8				
Mean±SD	12.77±10.55	13.05±10.62	205.72±338.73	219.95±422.65
Median (IQR)	11 (7,16)	12.5 (7.5,18)	88 (45,221)	106 (41,256)
9				
Mean±SD	12.4±9.72	14.98±11.03	185.89±291.71	259.04±450.85
Median (IQR)	11 (7,17)	13 (9,20)	99 (35,214.5)	132 (63,252)
10				
Mean±SD	13.17±10.57	15.29±11.1	211.93±369.46	267.76±455.49
Median (IQR)	11 (7,18.5)	13 (9,19)	97.5 (35,229.5)	148 (54,304)
11				
Mean±SD	12.38±9.77	15.42±11.49	175.38±263.23	277.23±453.95
Median (IQR)	11 (6,18)	14.5 (8,22)	89 (30,240)	160 (48,304)
12				
Mean±SD	12.7±10.61	14.43±12.59	177.42±273.07	263.78±473.41
Median (IQR)	11 (9,17)	14 (5,20)	90 (54,204)	140 (20,276)
13				
Mean±SD	12.39±11.57	14.9±10.93	192.2±309.43	284.9±513.78
Median (IQR)	11 (5,17)	12.5 (10.5,19.5)	84 (15,221)	112.5 (75,321.5)
14				
Mean±SD	10.11±8.99	17.46±13	130.57±175.95	342.62±592.25
Median (IQR)	10 (0,16)	13 (11,23)	80 (0,180)	130 (88,276)

Table 3

variable		P of t14 vs t1
longest diameter		
	HR+	0.387
	HR-	0.929
	With LN metastasis	0.058
	Without LN metastasis	0.368
	Tumor occurred during chemotherapy	0.880
	Tumor occurred after chemotherapy	0.068
	Drug A only	0.918
	Drug B only	0.049 *
	Other drugs	0.866
Long diameter × short diameter		
	HR+	0.567
	HR-	0.350
	With LN metastasis	0.330
	Without LN metastasis	0.210
	Tumor occurred during chemotherapy	0.488
	Tumor occurred after chemotherapy	0.068
	Drug A only	0.776
	Drug B only	0.156
	Other drugs	0.866
difference in longest diameter		
	HR+	1.000
	HR-	0.683
	With LN metastasis	0.611
	Without LN metastasis	0.600
	Tumor occurred during chemotherapy	0.532

	Tumor occurred after chemotherapy	0.068
	Drug A only	0.570
	Drug B only	0.090
	Other drugs	0.068
difference in long diameter× short diameter		
	HR+	0.993
	HR-	0.799
	With LN metastasis	0.874
	Without LN metastasis	0.807
	Tumor occurred during chemotherapy	0.396
	Tumor occurred after chemotherapy	0.068
	Drug A only	0.394
	Drug B only	0.035 *
	Other drugs	0.028 *

Figures

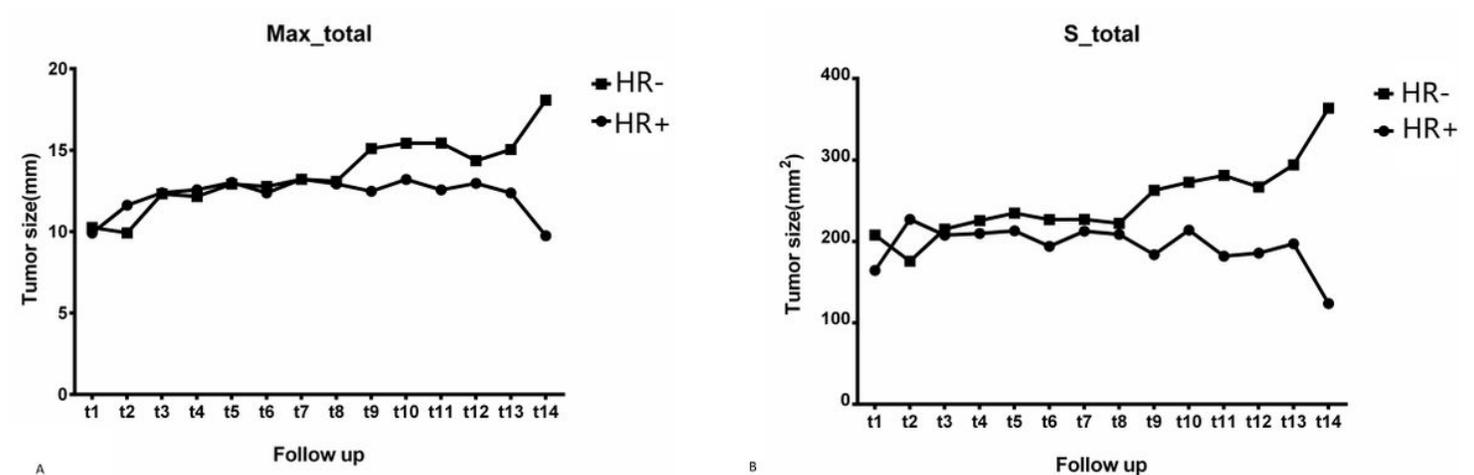


Figure 1

A Longest diameters of hepatic hemangiomas in the experimental and control groups B Long diameters × short diameters of hepatic hemangiomas in the experimental and control groups

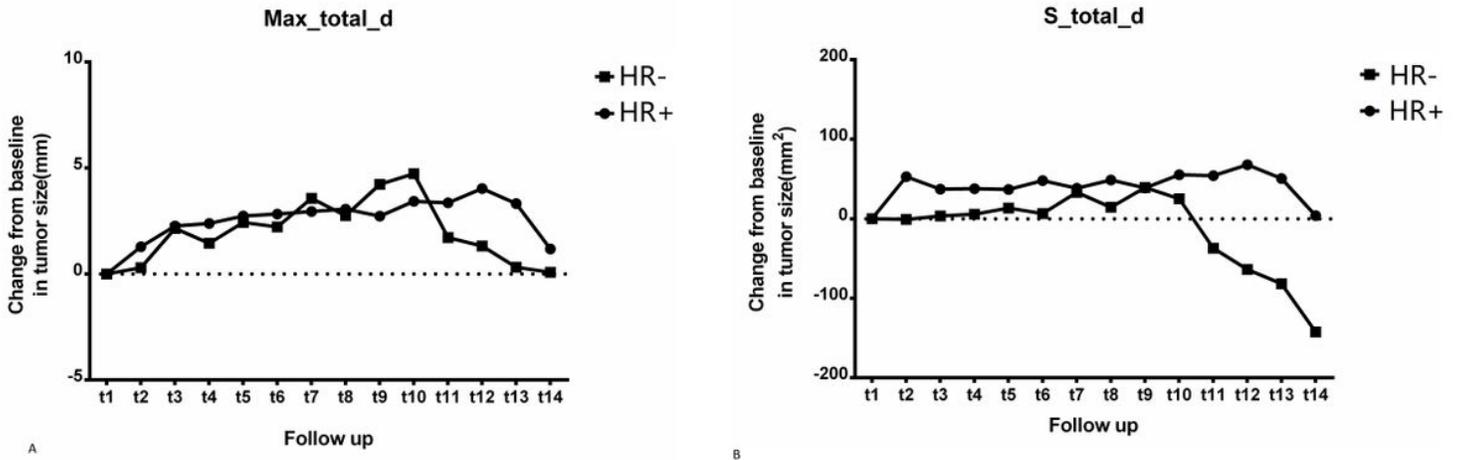


Figure 2

A Differences in size change (longest diameter) for hepatic hemangioma at different time points
 B Differences in size change (long diameter x short diameter) for hepatic hemangioma at different time points; *P<0.05

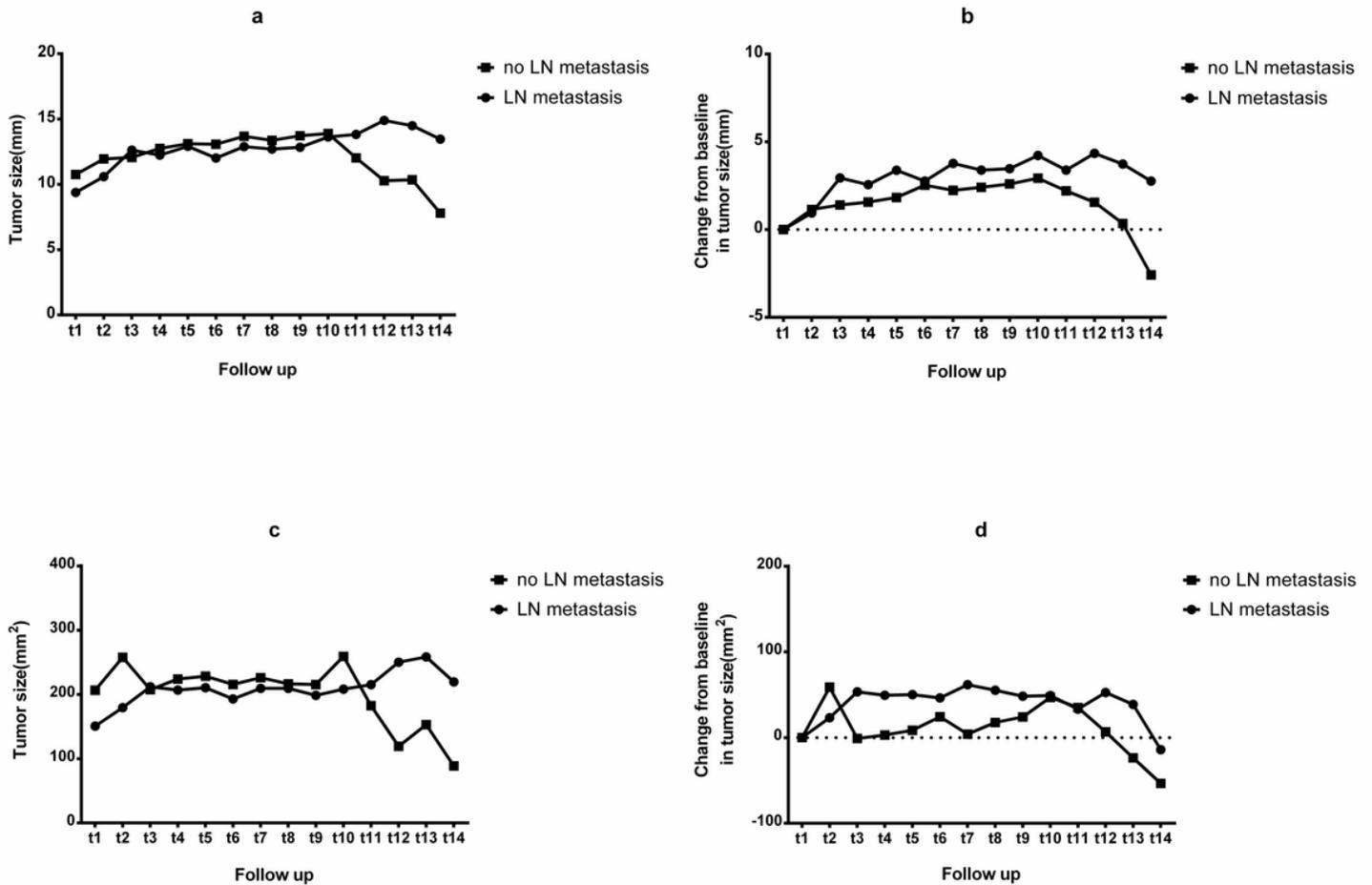


Figure 3

Relationship between lymph node metastasis of breast cancer and the size change of hepatic hemangiomas Fig. 3A Relationship between lymph node metastasis and the size (longest diameter) change of hepatic hemangiomas in breast cancer. Fig. 3B Difference between lymph node metastasis and the size (longest diameter) change of hepatic hemangiomas in breast cancer. Fig. 3C Relationship between lymph node metastasis and the size (long diameter x short diameter) change of hepatic hemangiomas in breast cancer; Fig. 3D Difference between lymph node metastasis and the size (long diameter x short diameter) change of hepatic hemangiomas in breast cancer.



Figure 4

Occurrence times and size changes of hepatic hemangiomas Fig. 4A Size (longest diameter) change of hepatic hemangiomas during and after chemotherapy. Fig. 4B Difference between the size (longest diameter) change of hepatic hemangiomas during and after chemotherapy. Fig. 4C Size (long diameter x short diameter) change of hepatic hemangiomas during and after chemotherapy. Fig. 4D Difference between the size (long diameter x short diameter) change of hepatic hemangiomas during and after chemotherapy; * P<0.05;**P<0.01; ***P<0.001.

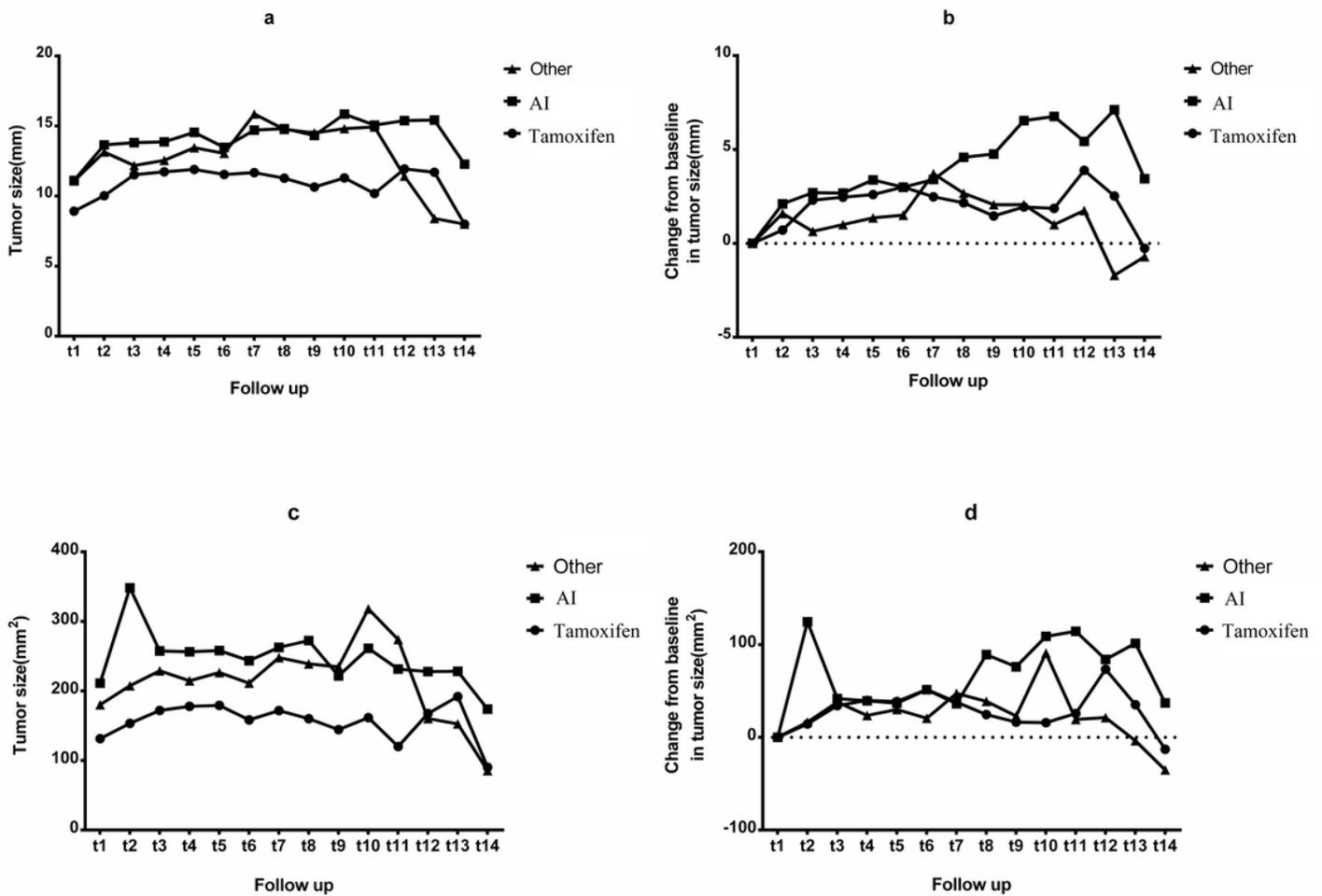


Figure 5

Relationship between the use of different endocrine drugs and the size of hepatic hemangiomas Fig. 5A Sizes (longest diameters) of hepatic hemangiomas after treatment with different endocrine drugs. Fig. 5B Changes in the size (longest diameter) of hepatic hemangioma after treatment with different endocrine drugs. Fig. 5C Sizes (long diameters × short diameters) of hepatic hemangiomas after treatment with different endocrine drugs. Fig. 5D Changes in the size (long diameter × short diameter) of hepatic hemangioma after treatment with different endocrine drugs. *P < 0.05; statistically significant difference after use of Drug B only versus other groups. Drug A, tamoxifen; drug B, AI.