

## Assessment of Ultrasonic Doppler Findings in Patients with Suspicious Preoperative Phyllodes Tumors

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### ABSTRACT

**Purpose:** In this prospective study, patients with preoperative suspicious phyllodes tumor based on several diagnostic imaging analyses were carried out ultrasonic color Doppler assessments. then investigated whether the ultrasonographic evaluation is available in differentiate malignancy.

**Subjects and Methods:** Subjects studied were 72 patients diagnosed ultrasonographic phyllodes tumor. They were divided into 5 groups based on pathological diagnosis of the surgical specimen or biopsy: 15 patients with benign phyllodes tumor, borderline phyllodes tumor (12 patients), malignant phyllodes tumor (4), fibroadenoma (31), breast cancer (10). Postoperative review was carried out, comparing ultrasonographic features included maximum flow velocity (Vmax), minimum flow velocity (Vmin), and resistance index (RI) levels between 5 groups.

**Results:** Onset ages in borderline and malignant phyllodes tumors were higher than those in fibroadenomas and breast cancers. Resistance Index (RI) levels in benign phyllodes tumors were, significantly lower than those in malignant phyllodes tumors and breast cancers. Maximal flow velocity levels in breast cancer were significantly higher than those in fibroadenoma, or benign phyllodes tumor (8.5+/-1.6cm/sec).

**Discussion:** It's difficult to make the ultrasonographic diagnosis in phyllodes tumors which are 2 cm or less in diameter to distinguish from fibroadenomas. Careful observation in internal echo lead irregular shaped cystic component to the suspected diagnosis in phyllodes tumors. Giant tumors are not always malignant, however, tumors characterized with enlarged, vascular rich, or accelerated proliferation are suspected to be malignant.

**Conclusion:** In this study of ultrasonic Doppler findings in phyllodes tumors, it is suggested that RI and maximal velocity levels in benign ones are significantly low compared with those in breast cancers or malignant phyllodes tumors. It's already known that RI levels greater than 0.8 are the evidence of malignant invasive cancers. It's necessary to evaluate whether the high RI levels in a phyllodes tumor are applied as a clinical index of malignant one. It's considered that furthermore studies in many cases are expected to clarify the diagnostic ultrasonic Doppler findings in phyllodes tumors whether those are malignant or not.

### Keywords

Phyllodes tumor, Ultrasonic color Doppler assessment, Fibroadenoma, Breast cancer, Resistance index (RI).

### Introduction

Incidence of phyllodes tumors are rare, less than 1% of all breast tumors [1]. The age of onset in patients with phyllodes tumors is

prominently higher than that in fibroadenoma. Their histological classification belongs to the mixed tumor that shows proliferation of the glandular epithelium and interstitial connective tissue, like that in the fibroadenoma.

The glandular epithelial component is stretched strongly and expand, resulting in a foliate structure. Phyllodes tumors are divided into 3 categories, such as benign, borderline, and malignant ones [2]. The remarkable findings of cellular heterotypic in interstitial non-epithelial components, cell density, and mitosis make malignant ones. However, epithelial components in malignant cases do not show malignant findings [3].

In this study, the maximum flow velocity (Vmax), the minimum flow velocity (Vmin), and resistance index (RI), obtained from the blood flow waveform analyses by pulsed Doppler method, were evaluated in the patients with preoperative suspicious phyllodes tumors, which had been diagnosed by various imaging analyses, then examined the possibility as a available tool for differentiation between benign and malignant phyllodes tumors.

## Subjects and Methods

From February 2006 to January 2010, 72 patients with suspicious phyllodes tumor were examined by preoperative ultrasonography at St. Marianna University School of Medicine. Pathological diagnosis of specimens by biopsy and surgery was divided into five groups such as 15 patients with benign phyllodes tumor, 12 with borderline phyllodes tumor, 4 with malignant phyllodes tumor, 31 with fibroadenomas and 10 with breast cancers. We got verbal informed consent, and conducted an examination within the scope of medical treatment.

The statistical correlation ship was examined comparing among the definite diagnostic 5 groups, preoperative finding of B-mode images and various parameters calculated from ultrasonographic analyses by the pulsed Doppler methods, such as maximum blood flow velocity (Vmax), minimum blood flow velocity (Vmin), resistance index (RI).

The ultrasonic diagnostic equipments were SSA -700 (Toshiba) and EUB-8500 (Hitachi) which central frequency of the probe was 8, 6 to 14 MHz linear electronic scanner. In B-mode examination, we observed the shape, depth width ratio, border, boundary echo, connective tissue spiculation, boundary line, internal echo and posterior echo of the tumor.

The ultrasonic diagnosis of phyllodes tumor was made like those which are characterized by a slit-shaped anechoic area, an ellipsoid, lobular round, or lobular shaped low echo tumor with smooth and unclear border, and the internal echo is homogenous. In another cases, the internal echo are occupied mainly fascination by fibroid component, however, heterogenous. Furthermore, we considered those showing internal cystic components, rather benign structure.

After confirming the blood flow wave by the color Doppler method, the pulse Doppler method was carried out. In the pulse

Doppler method, the velocity range is adjusted according to the maximum flow velocity of the blood vessel starting from the initial value of 5 cm/s, the wall filter is set to low, the sampling volume is adjusted from the initial value 2 mm according to the blood vessel diameter. The angle correction is set to 60 ° or less, then search the waveform with carefully not to press the affected part. The tracing of the blood flow waveform was carried out by automatic measurement.

We measured Vmax, Vmin and peripheral circulatory resistance index RI levels in intra-tumoral vessels and, then compared among 5 groups [4]. The difference of average values value between the 2 groups was tested by Mann-Whitney U test (IBM SPSS statics: test of 2 independent samples).

Examinations were conducted with patients' approval within the scope of routine examinations. All procedures were in accordance with the ethical standards of the respective committees (institutional and national) on human experimentation and with the 1964 Declaration of Helsinki and later versions.

## Results

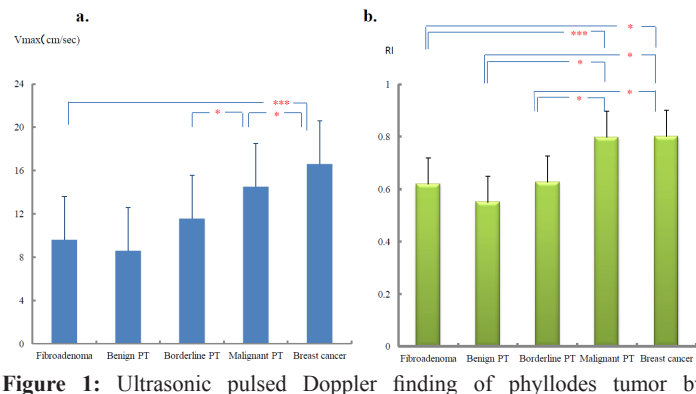
In the preoperative ultrasonic examination, 72 patients were suspected phyllodes tumor. The pathologically definite diagnoses in 72 patients were 15 benign phyllodes tumors (20.8%), 12 borderline phyllodes tumors (16.7%), 4 malignant phyllodes tumors (5.6%), 31 fibroadenomas people (43.1%), 10 breast cancers (13.8%). The breast cancers were including 1 mucinous carcinoma and 9 ductal carcinomas.

### Age

The age in patients with malignant phyllodes tumor was 52.8 +/- 11.1 year-old (average +/- standard deviation), was significantly higher than that in fibroadenoma (29.8 +/- 11.1 year-old,  $p < 0.0005$ ), benign phyllodes tumor (30.7 +/- 7.7 year-old,  $p < 0.0002$ ) and breast cancer (38.7 +/- 6.7 year-old,  $p < 0.0132$ ). The age in patients with borderline phyllodes tumors (44.4 +/- 7.9 years) was significantly higher than that in fibroadenoma ( $p < 0.0002$ ) and benign phyllodes tumor ( $p < 0.0001$ ). The age in patients with breast cancer was significantly higher than that in fibroadenoma ( $p < 0.0198$ ) and benign phyllodes tumor ( $p < 0.0118$ ).

### Maximum flow velocity of intra-tumoral vessels

The Vmax of intra-tumoral blood vessels in patients with breast cancer was 16.6 +/- 1.8 cm / s (average value +/- standard error) (Figure 1a, Figure 2), that in patients with all the kind of phyllodes tumor 10.3 +/- 1.6 cm/s (Figure 1a, 3), and fibroadenoma 9.5 +/- 0.8 cm/s (Figure 1a, Figure 3). The V max in patients with breast cancer was significantly higher than that in patients with fibroadenoma ( $p < 0.0015$ ). The Vmax in patients with malignant phyllodes tumor was 14.5 +/- 3.8 cm/s (Figure 1a, Figure 4 and significantly lower than that in patients with breast cancer ( $p < 0.02$ ), further significantly higher than that in patients with borderline phyllodes tumor (11.5 +/- 3.1 cm/s,  $p < 0.05$ ) (Figure 1a, Figure 5). The Vmax of the benign phyllodes tumor was 8.5 +/- 1.6 cm / sec (Figure 1a, Figure 6).

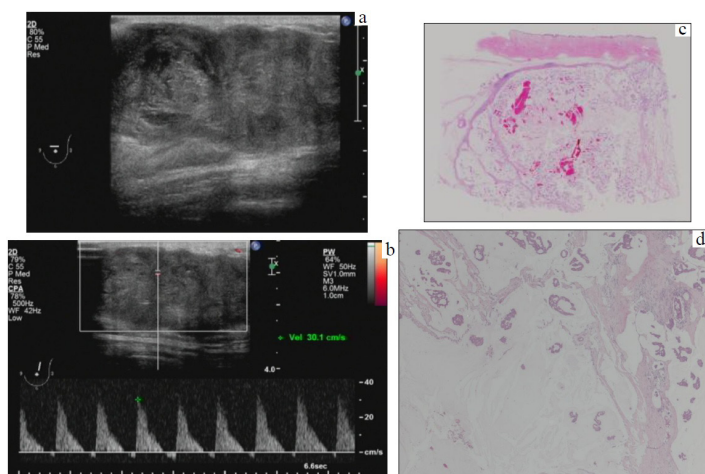


**Figure 1:** Ultrasonic pulsed Doppler finding of phyllodes tumor by preoperative ultrasonic diagnostic examination.

**a.** Maximum velocity (Vmax) of intra-tumoral artery.

**b.** Resistance index of intra-tumoral artery.

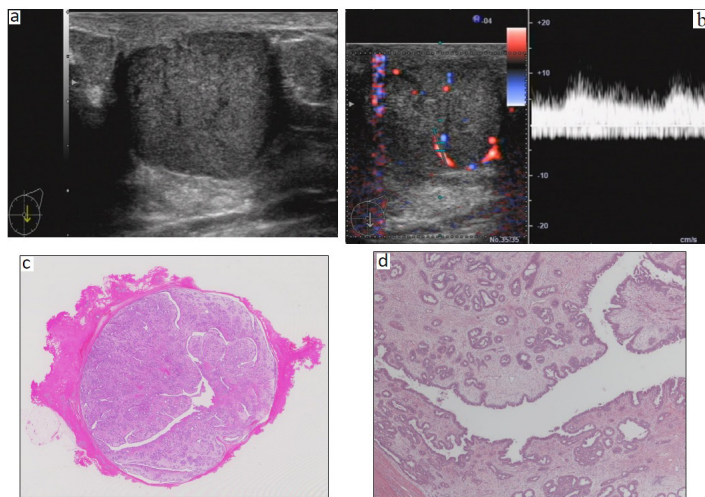
Error bar: SE, \* :  $p < 0.05$ , \*\*\*:  $p < 0.0005$ .



**Figure 2:** Mucinous tumor, pure type, in 49 year-old patient.

**a, b:** Ultrasonographic finding: Lobular mass sized more than 50mm in transverse diameter, 24mm in longitudinal diameter. It showed clearer border, and flat multiple nodular tumor. Mobility with the pectoralis major was good, internal echo was heterogenous, a part of anechoic area was found. There were multiple small cystic area in bilateral breast. RI: 1.0, Vmax: 23.5 cm/s

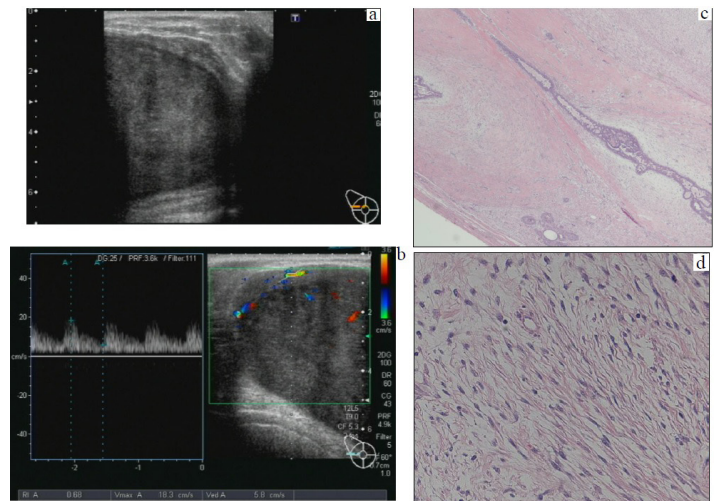
**c, d:** Pathological features: The tumor in the left AC region was sized  $6.0 \times 5.0 \times 3.5$  cm, well-defined, containing mucous in internal area, and tumor cell agglomerates with nuclear atypia are floating in a large amount of mucous stored outside the cells.



**Figure 3:** Fibroadenoma organoid type in a 22 year-old patient.

**a, b:** Ultrasonographic findings: A space occupied lesion of  $22 \times 21 \times 17$  mm in ECD area of left breast showed clear bordered ellipsoid, and low echoic mass with relative homogenous internal echo. The internal echo contained linear echo with fibrous septal structures. This linear echo is observed when the backscattering is enhanced in the region where the acoustic impedance difference is large in the boundary between the duct and the fibrotic interstitial tissue. In addition, fibrotic septum structure is rare in the inside of fibroadenoma, and it is not seen in this case histopathology. Blood flow is abundant. RI: 0.67, Vmax: 9.9 cm / s

**c, d:** Pathological features: The tumor was glandular epithelial components rich, and also rich in blood flow. The interstitial tissue consists of mild proliferation of fibroblasts and dense collagenous fibers.

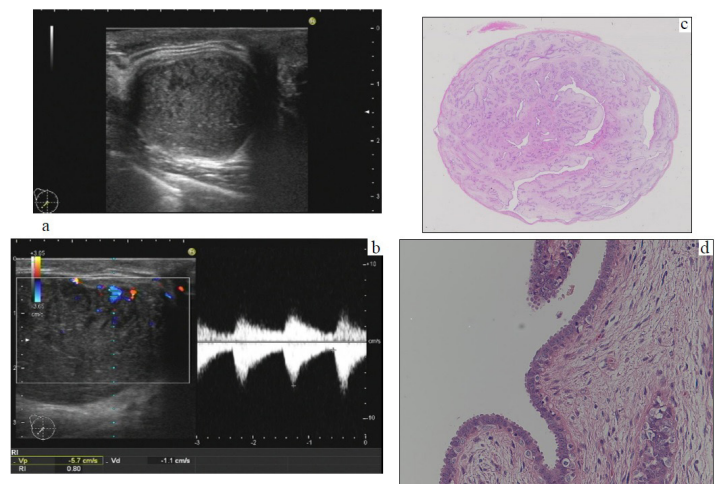


**Figure 4:** Malignant phyllodes tumor in a 58 year-old patient.

**a, b:** Ultrasonographic findings: There was a clear bordered, lobular tumor sized more than 8 cm in right breast CD region. It contained a slit like anechoic area. RI: 0.68, Vmax: 18.3 cm / s

**c, d:** Pathological features: The resected tumor was sized in  $9.5 \times 9.0 \times 8.0$  mm, covered with fibrous connective tissue and adipose tissue, showed yellowish-white and solid contents, the part of which had bleeding. Histologically, at the periphery of the tumor, there was an image of a phyllodes tumor consisting of dilatation of lumen and mild proliferation of epithelium and proliferation of breast duct-like structures and proliferation of stromal tissue. The center of the tumor was solid tumorous lesion consisting of fibroblast-like spindle cell proliferation and somewhat myxoma-like stroma, with scattering proliferating cells in a mitotic stage.

The interstitial component showed especially a finding equivalent to myxofibrosarcoma, low grade.

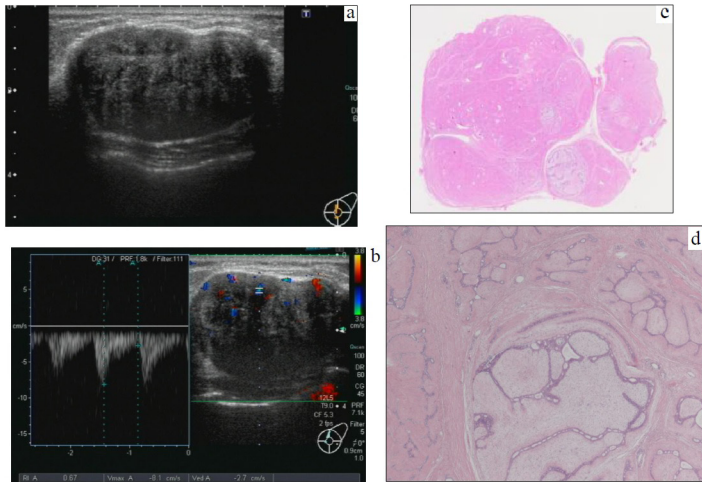




**Figure 5:** Border-line phyllodes tumor in a 48 year-old patient.

**a, b:** Ultrasonographic findings: A lobular ellipsoid tumor of size  $37 \times 24 \times 18$  mm was observed in the 8 o'clock direction of the right breast and a slit-shaped anechoic area was observed in the internal echo. Blood flow is abundant, RI: 0.61, Vmax: 6.4 cm / s.

**c, d:** Pathological features: The clear bordered tumor was low density in cells, however the nuclear fission feature was slightly higher at 5/10 HPF (high power field).



**Figure 6:** Benign phyllodes tumor hemorrhage in a 23 year-old patient.

**a, b:** Ultrasonographic findings: The lobular ellipsoid tumor sized in  $47 \times 46 \times 27$  mm in the left breast E region was clear bordered, smooth marginal. The internal echoes are relatively low, and showed slit-like structures. Blood flow entering the mass was relatively abundant. RI: 0.36 - 0.67, Vmax: 3.4 - 14.8 cm / s.

**c, d:** Pathological features: The mass was white, solid, and clear bordered. The edematous fibrous interstitial tissue around the duct was proliferated accompanied by depression of the duct. The cell density was low and the nuclear fission images was also 0-1 / 10 HPF.

#### Minimum flow velocity of intra-tumoral blood vessel

The Vmin of the intra-tumoral vessels in patients with fibroadenoma was  $3.5 \pm 1.2$  cm / s, that in patients with benign phyllodes tumor  $3.9 \pm 0.6$  cm / s, that in patients with borderline phyllodes tumor  $4.3 \pm 1.1$  cm / s,  $3.7 \pm 2.1$  cm / s (malignant phyllodes tumor),  $2.9 \pm 0.9$  cm / s (breast cancer), and the Vmin showed no significant difference among the groups.

#### Resistance Index (RI)

The RI of intra-tumoral vessels was  $0.80 \pm 0.09$  (mean  $\pm$  standard error) (breast cancer),  $0.619 \pm 0.024$  (all the kind of phyllodes tumor),  $0.61 \pm 0.02$  (fibroadenoma), and the RI in patients with breast cancer was significantly higher than that in patients with phyllodes tumor ( $p < 0.0158$ ) and fibroadenoma ( $p < 0.0093$ ).

The RI in patients with malignant phyllodes tumor was  $0.79 \pm 0.05$ , and was significantly higher than those in patients with benign phyllodes tumors ( $0.55 \pm 0.04$  ( $p < 0.05$ ), borderline phyllodes tumors ( $0.62 \pm 0.03$  ( $p < 0.05$ ), and fibroadenomas ( $p < 0.005$ ) (Figure 1b). The RI in patients with malignant phyllodes tumor showed no significant difference compared with that in

patients with breast cancer.

Pathological diagnoses of breast cancer cases were 2 cases of papillotubular carcinoma, 2 cases of solid-tubular carcinoma, 2 cases of scirrhous carcinoma, 1 case of spindle cell carcinoma, 1 medullary carcinoma and 2 cases of mucinous carcinoma.

#### Discussion

The phyllodes tumor is a solid tumor with a cystoid part including macroscopic lobular protrusions, which shows, resembling fibroadenoma, a hard and boundary clear lobular ellipsoid shape developing inflatable and its color is pale white to yellow-brown. While a part of fibroadenomas are accompanied by degeneration, necrosis, infarction, and bleeding, phyllodes tumors are abundant with the interstitial components and cellular components and the tumor occasionally has a huge diameter of more than 5 cm [1].

Mammography findings of phyllodes tumors, as the other diagnostic imaging analyses, showed equal to high concentration of circular or lobular mass with clear border lining. The ultrasonic preoperative diagnosis of phyllodes tumor was carried out based on findings such as slit shaped anechoic area, clear border-lined smooth surfaced ellipsoid or lobular round or lobular low echoic legion, which internal echo was homogenous, while those containing large sized, amount of fibrous fascination structure with heterogeneous internal echo. Furthermore, internal cystic components can be a sign of the relatively benign structured tumor [5]. As a tumor with less than 2 cm in diameter is especially difficult to distinguish from a fibroadenoma, we carefully observed the internal echo, and if there is an irregular shaped cystic component, we suspect it a phyllodes tumor. Although the large tumor may sometimes be benign, but we usually considered it malignant tumor to be large, blood flow rich and show rapid proliferation [6,7].

As a result, in the diagnosis by the ultrasonic B-mode method and the color Doppler method (RI), 43.0% of 72 patients with ultrasonographic phyllodes tumors were those with fibroadenomas, 43.0% were phyllodes tumors, and 13.9% were breast cancer. Forty percent of patients with breast cancer are classified as special type, in this time we showed a case of mucinous carcinoma. A fibroadenoma is easy to be misdiagnosed as a phyllodes tumor in preoperative ultrasonography, and a fibroadenoma is easy to be misdiagnosed as a mucinous carcinoma, therefore a mucinous carcinoma is easy to be misdiagnosed as a phyllodes tumor [8,9]. We studied that the pulsed Doppler method is useful as a diagnostic support mean. In the ultrasonic pulse Doppler method, the pulsatility index (PI) is defined as the value obtained by dividing the difference between Vmin and Vmax by the average blood flow velocity Vmean per a heartbeat. That is, the value changes depending on the heart rate. In addition, it may be a factor to increase an error that PI values measurements are necessary to trace the waveform manually. These are reason why we did not use PI, but RI. The, Vmax and Vmin values were also measured as a detectable marker. As a result, it was shown that RI is significantly higher in malignant phyllodes tumors and breast cancers than in fibroadenomas, benign phyllodes tumors, and borderline phyllodes

tumors. In addition, breast cancers showed that the highest flow rate was significantly higher than malignant phyllodes tumors.

As described above, the study of B-mode ultrasonic phyllodes tumor was carried out pulsed Doppler measurement and calculated Vmax and RI. As a result, RI levels in B-mode phyllodes tumor are rather lower than those in breast cancers. The ultrasonographic comparison between phyllodes tumors and fibroadenomas is not available, and the additional information of V max and RI in vain.

It is suggested that Vmax and RI obtained by pulse Doppler method may be useful B-mode ultrasonic phyllodes tumors for distinguishing among malignant, borderline and benign tumors. Chao et al. [9] demonstrated that the diagnosis of phyllodes tumors by ultrasonic B-mode is based on lobular tumor with the smooth surface, lower internal echo, heterogenous internal echo without calcification. In addition, 51.4% of patients show more than 0.7 RI levels, and 51.4% of patients show more than 15 cm / s of Vmax.

Park HL, et al. [10] reported that phyllodes tumors show the round to ellipsoid tumors without calcification, and with heterogenous and cystoid internal echo by ultrasonic B-mode scanning, then the vacuum-assisted biopsy was carried out. They demonstrated a conclusion that a long-term follow-up and observation is necessary even if they were benign phyllodes tumors.

Bernardi G et al. [11] diagnosed as a phyllodes tumor the case of which smooth marginal round shaped tumors with posterior echo enhancement or attenuation by ultrasonic B-mode scanning, and intra-tumoral vessels by color-Doppler methods. They reported that it was difficult to discriminate whether it is malignant one or not.

Mishra SP et al. [12] used ultrasound diagnosis and defined the phyllodes tumors that show the smooth marginal round or lobular tumors with heterogenous internal echo and fasciation structure, including higher values of RI, PI, Vmax.

In addition, Hayashi et al. [13] reported that PI and RI were high in malignant breast tumors,. Okuno et al. [14] measured PI and RI using ultrasonic Doppler method to differentiate between breast cancer and benign tumors, then proposed that it frequently happens to be the malignant tumors with more than 1.3 of PI and more than 0.74 of RI.

In these papers, they demonstrated that PI and RI have overlapping parts between benign and malignant ones, so the B-mode scanning are inevitable for the confirmed diagnoses. The wave form of breast cancers are higher themselves, because pathological features of intra-tumoral blood vessels in breast cancers proliferated among hard fibrous interstitial tissues, and deficiency of elastic fibers, then showed an increase of blood flow volume.

As a result, although higher flow velocity is shown during systole, the reflux pressure in diastole is low and the flow velocity is low. Therefore, the blood flow waveform becomes sharp and RI shows

a high value. On the other hand, in fibroadenomas and benign phyllode tumors, although vascular hyperplasia is observed, they keep anatomical structure, and neoplastic changes in surrounding interstitial tissues are poor and do not significantly effect on blood flow velocities. There is no increase in blood flow as much as breast cancer, and the blood flow waveform shows relatively low in systole, relatively high in diastolic.

Although malignant phyllodes tumor is rare and is not well known about its blood flow dynamics, but pathologically does not contain elastic fiber, surrounding interstitial tissues are not so hard as breast cancer, which is the reason why PI and RI levels of malignant phyllodes tumors are intermediate values between those of fibroadenoma and breast cancer. The blood flow volume increase followed by an increases of Vmax values in patients with malignant phyllodes tumors may be shown so much as those with breast cancers.

The diagnoses of breast tumors are usually carried out by ultrasonic B-mode examination based on the other clinical findings, such as age, inspection and palpation findings, mammography findings, etc. Taking it into account how the traditional diagnostic methods by B-mode scanning can be, it's an important point that additional technique of pulsed Doppler methods may improve diagnostic ability or not.

Some of Vmax, Vmin and RI values show statistically significant differences among breast cancers, phyllodes tumors, and fibroadenomas, however it's unknown how they contribute to diagnostic ability. It is necessary to verify whether these values are clinically effective or not, whether diagnostic ability can be improved by successfully combining with B-mode diagnosis, or whether these techniques can be available to malignant phyllodes tumor. It needs to followed up by increasing the number of subjects.

In this study, we examined whether malignancy of phyllodes tumor can be judged by pulsed Doppler findings as a preliminary trial, however further examination is expected in future cases.

## Conclusion

In this study of ultrasonic Doppler findings in phyllodes tumors, it is suggested that RI and maximal velocity levels in benign ones are significantly low compared with those in breast cancers or malignant phyllodes tumors. It's already known that RI levels greater than 0.8 are the evidence of malignant invasive cancers. It's necessary to evaluate whether the high RI levels in a phyllodes tumor are applied as a clinical index of malignant one. It's considered that furthermore studies in many cases are expected to clarify the diagnostic ultrasonic Doppler findings in phyllodes tumors whether those are malignant or not.

## Human rights statements and informed consent

Examinations were conducted with patients' approval within the scope of routine examinations. All procedures were in accordance with the ethical standards of the respective committees (institutional and national) on human experimentation and with the 1964

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Declaration of Helsinki and later versions. The institutional review board (IRB)/ Ethics Committee of Yokohama Leaf Minatomirai Health Care Clinic has ruled that approval was not required for this retrospective study.

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