Does Color Doppler Ultrasound Vascularity Predict the Response to Neoadjuvant Chemotherapy in Breast Cancer?

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Objectives: *To assess the proportions of response to neoadjuvant chemotherapy of breast cancer according to color Doppler ultrasound vascularity patterns.*
Material and Method: *Prospective evaluation using gray scale and color Doppler ultrasound for number of vessels and feeding appearances of tumors as well as the changes in tumor sizes at before and after chemotherapy in 69 breast cancer patients.*
Results: *The overall response rate in 70 breast cancers was 20%. Twenty-nine lesions (41%) showed hypervascularity and 41 lesions (59%) revealed hypovascularity. There were 5 vascularity patterns and each pattern had the proportion of responders as follows; 33.3% for hypovascularity with single-vessel feeding into the tumor, 25% for hypovascularity with single-vessel feeding at periphery of the tumor, 25% for no vascular feeding to the tumor, 16.7% for hypervascularity with vascular feeding at the periphery of the tumor and 13% for hypervascularity with vascular feeding into the tumor. The highest percentage of responsive group was the pattern of hypovascularity with single-vessel feeding into the tumor (33.3%).*
Conclusion: *There is a trend that tumor vascularity and patterns of vascular feeding by color Doppler ultrasound can predict the responsiveness of breast cancer to neoadjuvant chemotherapy.*

Keywords: *Breast cancer, Color doppler, Imaging, Neoadjuvant, Tumor response*

J Med Assoc Thai 2005; 88 (10): 1367-72
Full text. e-Journal: *http://www.medassocthai.org/journal*

Breast cancer is one of the leading causes of mortality among women in the world today and is the most prevalent cancer among women throughout the world. The actual cause of breast cancer is still unknown and is probably due to multitude of factors(1). In Thailand, breast cancer is the second most common malignant tumor after cervical cancer and also the second cause of cancer death in females. The number of new cases has been increasing; the most recent incidence is at 17.2 per 100,000 women(2).

Neoadjuvant chemotherapy is given before surgery. The major benefit is that it often shrinks the cancer so that the mass can be removed; otherwise it would be too large for complete surgical removal. This is particularly useful for breast conservation treatment(3).

Tumor vessels are structurally and functionally abnormal. It is established that the degree of vascularity can determine the tumors' aggressiveness, as well as their radiosensitivity and chemosensitivity(4). A decrease in tumor vascularity might indicate a response to therapy, while an increase or no change in vascularity might predict a failure to response. Doppler sonography has been routinely used for the assessment of tumor vascularity(5-8). Nevertheless, a simple classification of patterns does not exist. The authors speculate that there would be differences in the rate of tumor responsiveness according to the number and patterns

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of vascular feeding. The figures might be useful for the management and for the comparison.

Material and Method

From January 2000 to December 2003, breast cancer patients treated with neoadjuvant chemotherapy at King Chulalongkorn Memorial Hospital were scheduled to have a pre-treatment and a short-interval post-chemotherapy ultrasound exam by using gray scale and color Doppler in order to assess the tumor response by radiological findings. Most patients received chemotherapy in the forms of CMF regimen (45 patients) and some patients with CEF regimen (24 patients) (C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, E = epirubicin). The follow-up ultrasound was performed after receiving 2-4 courses of neoadjuvant chemotherapy. All of the ultrasound images were evaluated by two radiologists of the authors.

The tumor responsiveness conformed to the WHO radiological criteria: *(a) Radiological complete response* (rCR) means radiologically no evidence of residual tumor, *(b) Partial remission (PR)* infers to reduction in the sum of the products of the maximum perpendicular diameters by 50% or more of all of the measurable lesion, no evidence of progression in any lesion and no new lesion, *(c) No response (NR) or stable* disease defines an increase in the size of the lesion by 25% or less or a decrease in the size by 50% or less in the sum of the products of the maximum perpendicular diameters of all of the measurable lesion, no evidence of progression in any lesion, and no new lesion *(d) Progressive disease (PD)* is for an increase in the sum of products by 25% or more of the maximum perpendicular diameters of all measurable lesions, and/or the appearance of a new lesion. To simplify an analysis, patients with complete or partial response were classified as "responders". Patients who showed no response or progressive disease were classified as "non-responders". In the present study, the tumor responsiveness was determined by the changes in tumor size on the ultrasound between before and after receiving chemotherapeutic drugs.

The tumor vascularity assessment was based on the number of feeding vessels. It was classified into 2 groups; hypervascularity meant two or more vessels were observed, and hypovascularity meant none or only one vessel was observed. The features of vascular feeding were divided into 2 patterns i.e. the vessels entering the tumor mass and vessels at the periphery. To combine the tumor vascularity and features of vascular feeding, five patterns were categorized as the following; *a) hypervascularity with vascular feeding into the tumor* (Fig. 1), *b) hypervascularity with vascular feeding at periphery of the tumor* (Fig. 2), *c) hypovascularity with single-vessel feeding into the tumor* (Fig. 3), *d) hypovascularity with single-vessel feeding at periphery of the tumor* (Fig. 4) *and e) no vascular feeding to the tumor.*

The tumor echogenicity was divided into homogeneous hypoechogenicity and heterogeneous hypoechogenicity. The posterior acoustics was divided into posterior enhancement and posterior shadowing.

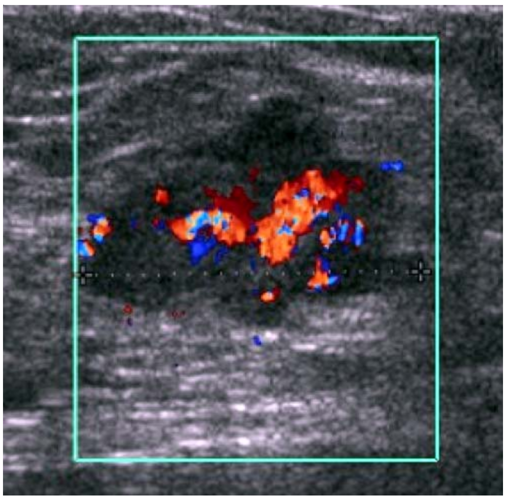

Fig. 1 A hypervascular tumor
Note a homogeneous hypoechoic lesion with posterior enhancement. The feature of vascular feeding into the mass is depicted

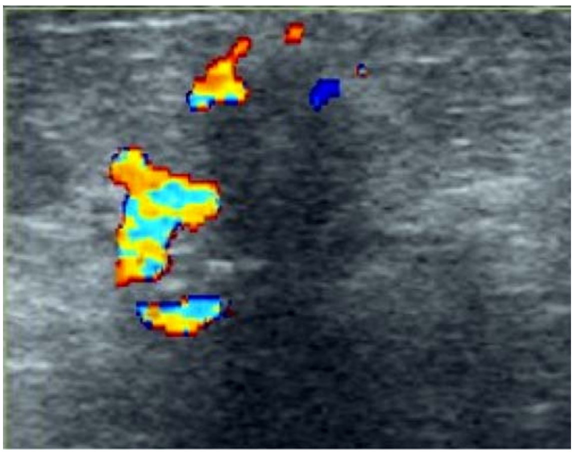

Fig. 2 A hypervascular tumor
Note a hypoechoic mass with posterior shadowing. The feature of vascular feeding at periphery of the mass is shown

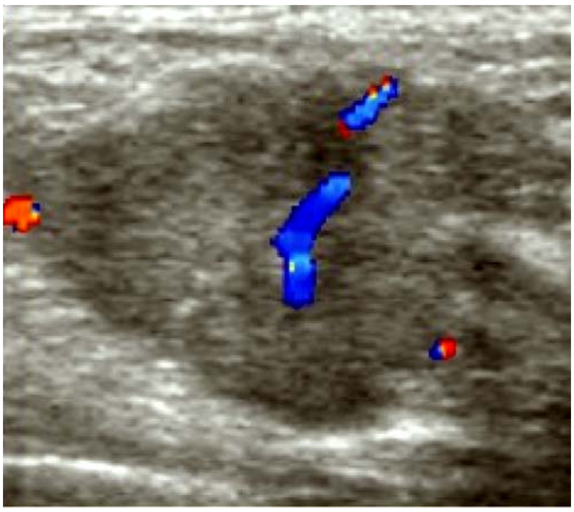

Fig. 3 A hypovascular tumor
Note a heterogeneous hypoechoic mass with posterior enhancement. There is a single vessel feeding into the mass

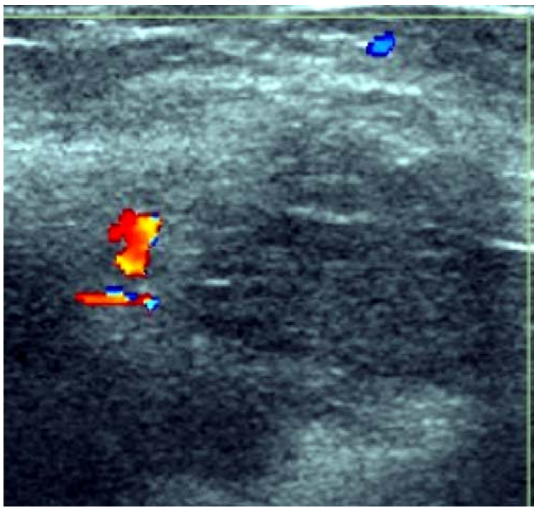

Fig. 4 A hypovascular tumor
Note a heterogeneous hypoechoic mass. There is a single vessel feeding at the periphery of the mass

Results

The study population comprised 69 women (70 breast malignant lesions) who ranged in age from 28 to 66 years (average 46.7 years). Post treatment ultrasound was done after 2 to 4 courses (average 2.7 courses) of neoadjuvant chemotherapy. The interval of the first and the second ultrasound was 11.5 weeks (3 to 24 weeks).

There were 29 lesions (41%) showing hypervascularity and 41 lesions (59%) hypovascularity. In the hypervascularity group, 23 lesions (79.3%) showed vascular feeding into the tumor while 6 others (20.7%) showed vascular feeding at the periphery. In the hypovascularity group, 21 lesions (51.2%) showed single-vessel feeding into the tumor, 16 lesions (39%) showed single-vessel feeding at the periphery and four lesions (9.8%) revealed no vascular feeding. The overall rates of the responder in the present study was 20% (Table 1). When the tumor showed hypervascularity, the prediction was 10.3% and when the tumor showed hypovascularity, it was 26.8%. The rates of tumor responsiveness in each vascular feeding category were as the following; a) hypervascularity with vascular feeding into the tumor = 13%, b) hypervascularity with vascular feeding at periphery of the tumor = 16.7%, c) hypovascularity with single-vessel feeding into the tumor = 33.3%, d) hypovascularity with single-vessel feeding at periphery of the tumor = 25% and e) no vascular feeding to the tumor = 25% (Diagram 1).

Eighty percent of the tumors showed heterogeneous hypoechogenicity. Both responder and non-responder groups had no differences in heterogeneous echogenicity, i.e.11 out of 14 (78.6%) and 51 out of 56 lesions (91.1%) respectively (Table 2).

Most of the tumors, 91.4%, showed posterior acoustic enhancement. In the responder group, all 14 lesions (100%) showed posterior enhancement. In the non-responder group, 6 out of 56 lesions (10.7%) showed posterior shadowing and 50 out of 56 lesions (89.3%) showed posterior enhancement (Table 3).

Regarding locations of the tumors, 36 lesions (51.4%) were located in the upper outer quadrant, 8 lesions (11.4%) in the upper inner quadrant, 7 lesions (10%) in the lower inner quadrant, and 2 lesions (2.9%) in the lower outer quadrant. The remaining 17 lesions (24.3%) were present at central, upper middle, lower middle, inner middle and outer middle areas.

Table 1. Vascularity and tumor responsiveness

Vascularity	Responder No. (%)	Non-responder No. (%)	Total No. (%)
Hypervascularity	3 (10.3)	26 (89.7)	29 (41)
Hypovascularity	11 (26.8)	30 (73.2)	41 (59)
Total	14 (20.0)	56 (80.0)	70 (100)

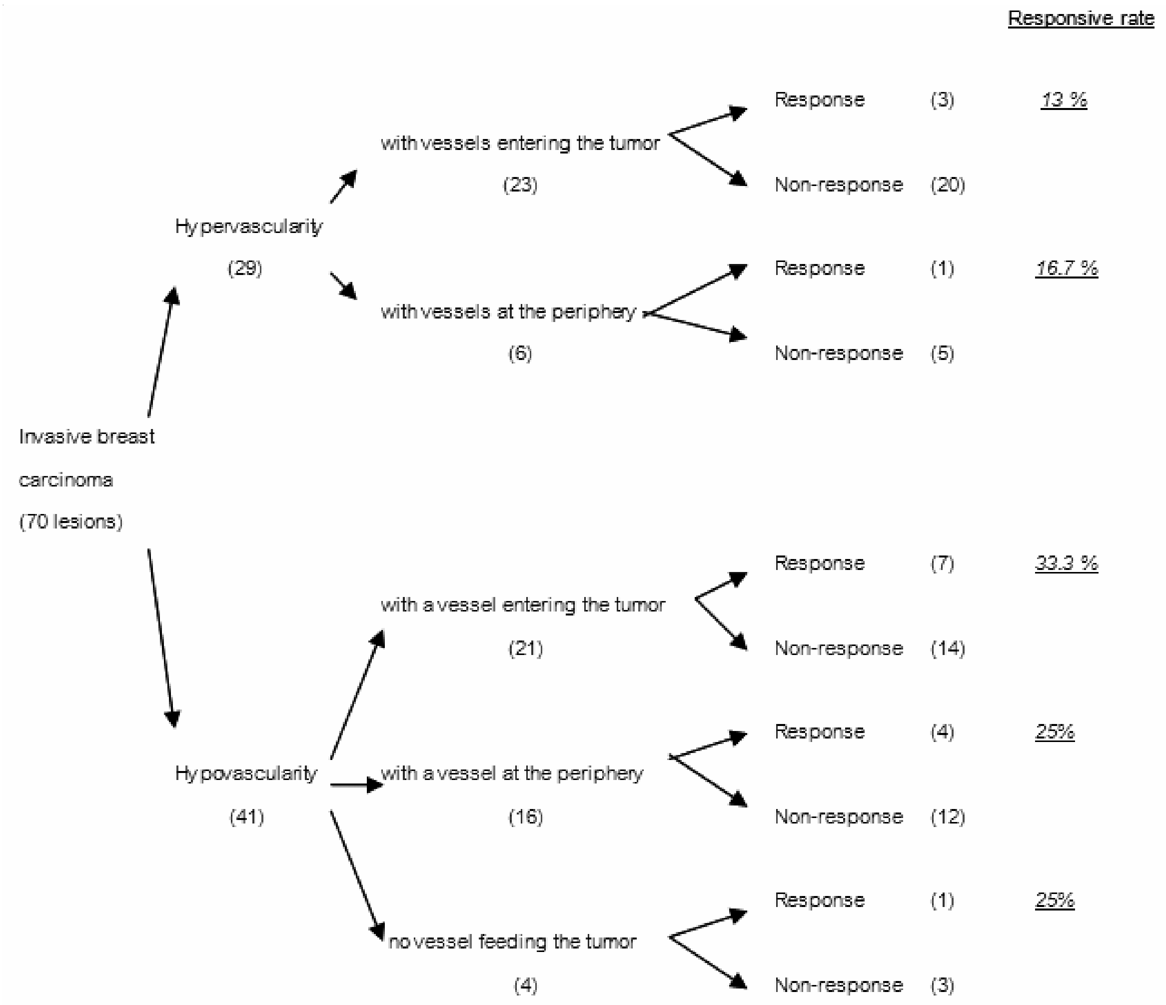

Diagram 1. Dichotomous tree of breast cancer lesions showing the number of tumor responsiveness to each color Doppler vascularity pattern

Table 2. Echogenicity of the tumors

Ultrasound findings	No. of cases (%)
Tumor hypoechoics	
Responder (n=14)	
- Homogeneous	3 (21.4)
- Heterogeneous	11 (78.6)
Non-responder (n=56)	
- Homogeneous	5 (8.9)
- Heterogeneous	51 (91.1)
Total (n=70)	
- Homogeneous	14 (20)
- Heterogeneous	56 (80)

Table 3. Posterior acoustics of the tumors

Ultrasound findings	No. of cases (%)
Posterior acoustics	
Responder (n=14)	
- Shadowing	0
- Enhancement	14 (100)
Non-responder (n=56)	
- Shadowing	6 (10.7)
- Enhancement	50 (89.3)
Total (n=70)	
- Shadowing	6 (8.6)
- Enhancement	64 (91.4)

The average tumor size was 2.6 x 1.7cm (maximum dimension ranged from 0.8- 3.9 cm) in the responder group and 2.7x1.6 cm^2 (maximum dimension ranged from 1.1- 3.6 cm) in the non-responder group.

Discussion

The concept that breast cancer is a systemic disease at presentation and may require medical treatment (with endocrine therapy or chemotherapy) along with or instead of surgery has become increasingly accepted[9-11]. Primary medical therapy in locally advanced cancers improves local control and surgical outcome offering a better cosmetics result as well as longer patient survival, while the combination with subsequent radiation therapy can avoid the need for mastectomy in most patients in whom it would otherwise have been required because of tumor size.

Response to medical therapy varies widely, some tumors shrink, a few respond minimally and others continue to progress. This unpredictability makes the choice of the appropriate treatment difficult and so, selection of the initial regimen is arbitrary and may need to be changed or abandoned, depending on clinical tumor response[9-11]. At King Chulalongkorn Memorial Hospital, most patients were started with CMF regimen; the others, particularly young patients were treated with CEF regimen. The overall tumor response (rCR and PR) of the present study was 20%.

To answer the question "*Does color Doppler ultrasound vascularity predict the response to neoadjuvant chemotherapy in breast cancer?*", the authors simply classified the tumor vascularity and patterns of vascular feeding into 5 categories by color Doppler ultrasound. If the rates of tumor responsiveness in each pattern are different, this could reflect the value in prediction. According to the present study, the hypervascular tumors had a lower probability on tumor response than the hypovascular group (10.3% vs 26.8%) (Table 1). Additionally, in the hypovascular group, the lesions with single-vessel feeding into the tumor had a higher rate of responders than those lesions with single-vessel feeding at the periphery of the tumor and lesions with no vascular feeding to the tumor (33.3% vs 25% vs 25% respectively). These results imply that tumor vascularity can predict tumor aggressiveness and tumor responsiveness to chemotherapeutic agents. The hypervasculity is predictor of tumor aggressiveness. The hypovascular group, particularly the lesions with single-vessel feeding into the tumor predicts a higher rate of response to neoadjuvant chemotherapy.

The other observations from the group of breast cancers in the present study are as follows. Firstly, the echogenicity of the tumors is mostly heterogeneous (80%); it cannot help to predicting tumor responsiveness. Secondly, nearly all of the breast cancers had posterior acoustic enhancement (91.4%); this finding does not help distinguishing responsive tumor from the non-responsive group. Finally, the breast cancers are usually located in the upper outer quadrant (51.4%).

Some limitations of the present study can be noted. Firstly, although the study was prospectively designed, the treatment regimens were not homogeneous. Most of the patients were treated with CMF regimen and some with CEF regimen either from the start or after clinical failed CMF. Secondly, there were limitations of the color Doppler evaluation, particularly when irregular or diffuse or marked posterior acoustic shadowing tumors were encountered. However, standard measurement criteria were conformed and a consensus was met by two radiologists. Finally, the sample size was relatively small, thus additional studies with adequate sample sizes are necessary.

In conclusion, there is a trend that tumor vascularity and patterns of feeding vessels by color Doppler ultrasound can predict the response of breast cancer to neoadjuvant chemotherapy. The rates of tumor response is higher when the tumor shows hypovascularity and single-vessel feeding into the tumor.

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ภาพหลอดเลือดของก้อนเนื้อมะเร็งจากการตรวจด้วยเครื่อง Doppler ultrasound สามารถทำนายการตอบสนองต่อการรักษาด้วยยาเคมีบำบัดก่อนการผ่าตัดในผู้ป่วยมะเร็งเต้านมได้หรือไม่

ดรุณี บุญยืนเวทวัฒน์, เจนจีรา ปรึกษาดี, พิเชฐ สัมปทานุกุล, กฤษณ์ จาฏามระ

วัตถุประสงค์: *เพื่อคำนวณสัดส่วนของการตอบสนองต่อการรักษาด้วยยาเคมีบำบัดก่อนผ่าตัดในผู้ป่วยมะเร็งเต้านมโดยลักษณะต่าง ๆ ของการเข้าไปเลี้ยงก้อนมะเร็งของหลอดเลือดโดย color Doppler ultrasound*

วัสดุและวิธีการ: *ทำการตรวจ ultrasound ด้วย gray scale และ color Doppler เพื่อดูจำนวนและลักษณะการเข้าไปเลี้ยงก้อนมะเร็งของหลอดเลือด และเปรียบเทียบขนาดของก้อนก่อนและหลังการให้ยาเคมีบำบัด ในผู้ป่วยมะเร็งเต้านมจำนวน 69 ราย*

ผลการศึกษา: *พบก้อนมะเร็งร้อยละ 20 จากจำนวน 70 รอยโรคมีการตอบสนองต่อยาเคมีบำบัด การตรวจด้วย ultrasound พบว่า 29 รอยโรค (ร้อยละ 41) อยู่ในกลุ่ม hypervascularity และ 41 รอยโรค (ร้อยละ 59) อยู่ในกลุ่ม hypovascularity การศึกษานี้ แบ่งลักษณะการเข้าไปเลี้ยงก้อนมะเร็งของหลอดเลือดเป็น 5 แบบ ซึ่งแต่ละแบบมีสัดส่วนของผู้ป่วยที่มีการตอบสนองต่อการรักษา ดังนี้ ร้อยละ 33.3 พบเป็น hypovascularity with single-vessel feeding into the tumor, ร้อยละ 25 พบเป็น hypovascularity with single-vessel feeding at periphery of the tumor, ร้อยละ 25 พบเป็น no vascular feeding to the tumor, ร้อยละ 16.7 พบเป็น hypervascularity with vascular feeding at periphery of the tumor, และ ร้อยละ 13 พบเป็น hypervascularity with vascular feeding into the tumor ผลการวิเคราะห์พบว่า กลุ่มที่มีการตอบสนองต่อการรักษาดีที่สุดคือ กลุ่มที่มีลักษณะ hypovascularity with single-vessel feeding into the tumor (33.3 %)*

สรุป: *มีแนวโน้มว่า ลักษณะของจำนวนและรูปแบบของหลอดเลือดที่เลี้ยงรอยโรคมะเร็งเต้านมโดย color Doppler สามารถใช้ทำนายผลการตอบสนองต่อยาเคมีบำบัดก่อนการผ่าตัดได้*