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Sonographic differentiation of invasive and intraductal carcinomas of the breast

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Abstract. The purpose of this study is to evaluate the diagnostic ability of ultrasound and define the sonographic features of symptomatic intraductal and invasive breast carcinoma. To achieve this the ultrasound features of 488 invasive carcinomas and 65 non-screening detected intraductal carcinomas were compared retrospectively. The features included size, AP/W (anteroposterior diameter/width) ratio, shape, margin, internal echogenicity, internal echotexture, posterior acoustic transmission, bilateral edge shadowing sign and calcifications. The sensitivity and specificity of the detection of calcifications by ultrasound in comparison with mammography were also studied. The accuracy of ultrasound diagnosis is 92.0% for invasive carcinoma of breast and 84.8% for intraductal carcinoma. Differentiation of ultrasound features of intraductal and invasive carcinoma can be based on the internal hypoechogenicity, loss of bilateral edge shadowing, posterior acoustic transmission, irregular shape and non-uniform internal echotexture with odds ratio of 0.3, 0.3, 0.4, 0.5 and 0.5, respectively. Internal echogenicity was the only significant differentiating factor on multiple logistic regression analysis. Non-comedo type ductal carcinoma *in situ* can be differentiated from comedo type by irregular shape with odds ratio of 0.3. The sensitivity, specificity and accuracy rate for the detection of calcifications in invasive carcinomas by ultrasound were 65.1%, 61.9% and 63.2%; in comedo type intraductal carcinoma 62.5%, 66.7% and 63.6%, and in non-comedo type intraductal carcinoma 30.0%, 86.7% and 64.0%, respectively. The ultrasound appearance of non-screening detected intraductal carcinoma is relatively isoechoic in comparison with invasive carcinoma. More than 60% of microcalcifications in comedo type intraductal carcinoma can be accurately demonstrated by ultrasound. However, the role of ultrasound in detecting symptomatic intraductal carcinoma warrants further study.

The incidence of intraductal carcinomas of the breast has increased dramatically since 1980 when screening mammography was widely adopted in Western nations [1]. In Taiwan, no screening program has been established so far, except for the high risk population [2]. The annual age-adjusted incidence rate of female breast cancer was 35 per 100 000 in 1998; intraductal carcinoma accounted for only 5% of total cases [3]. In this hospital, the incidence rate of intraductal carcinomas increased from 4.1% in 1990 to 8.3% in 1998. The challenge of intraductal carcinoma lies not only in its treatment, but also in the diagnosis, owing to its tendency to produce subtle mammographic findings in the dense Chinese female breast [4].

Ultrasound plays a major role in the differentiation of benign and malignant breast neoplasms in women aged 40 years or younger and in oriental female patients [5, 6]. However, to date, the use of ultrasound for population screening of asymptomatic women has been reported to show high rates of both false positive and false negative results [7, 8], along with poor detection of microcalcifications, an important feature of both intraductal carcinoma and small invasive cancer [9, 10]. Here we present the ultrasound features of both invasive and intraductal carcinoma of the breast including the detection rate of microcalcifications in Chinese women. The purpose of our study was to define the ultrasound features of palpable intraductal carcinoma and to help in establishing the role of ultrasound as an adjunct screening modality to X-ray mammography.

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Materials and methods

We reviewed the ultrasound records in the hospital database from 1996 to 1999. Only the reports of ultrasound examinations performed by the author (SCC) were selected for the study to eliminate reading bias. The author performed breast ultrasound without knowledge of mammographic findings and ultrasound features were recorded by computer prospectively. In the 4 consecutive years, cases with pathological proven malignancy with available X-ray mammography were included in the study. There were 488 invasive carcinomas and 65 intraductal carcinomas included. All the lesions had histological confirmation after excisional biopsy.

All the patients in this study who visited the clinic with a palpable mass, subtle nodule or mastalgia had both ultrasound and X-ray mammographic examinations. Ultrasound was performed using a high resolution (7.5–10 MHz) probe with the Aloka SSD-2000 ultrasound unit (Aloka, Tokyo, Japan) or HDI 5000 (Advanced Technology Laboratories, Bothell, WA). Whole breast ultrasound was undertaken. The ultrasound appearances were evaluated with regard to shape, margin, internal echogenicity, internal echotexture, posterior acoustic transmission, edge shadowing, presence of microcalcifications,

number of vessels detected in colour Doppler examinations and the AP/W (anteroposterior diameter/width) ratio as previously described [11]. The AP/W ratio indicated the anteroposterior dimension divided by transverse dimension sonographically. The shape was classified as round/oval, lobulated or irregular; the margin was classified as smooth or irregular; internal echogenicity was categorized as hyperechoic, isoechoic or hypoechoic; internal echotexture distribution was categorized as uniform or non-uniform; posterior acoustic transmission was classified as enhancement, neutral or shadowing; bilateral edge shadowing was categorized as present or not; the presence of calcifications was classified as yes or no, and the detection of calcifications by ultrasound was confirmed with the findings of X-ray mammography. Mammography was used as the gold standard for the presence of microcalcifications, because pathological reports did not usually mention it. All film–screen mammograms were performed using the LORAD MIV mammographic unit (LORAD, Danbury, CT).

Statistics

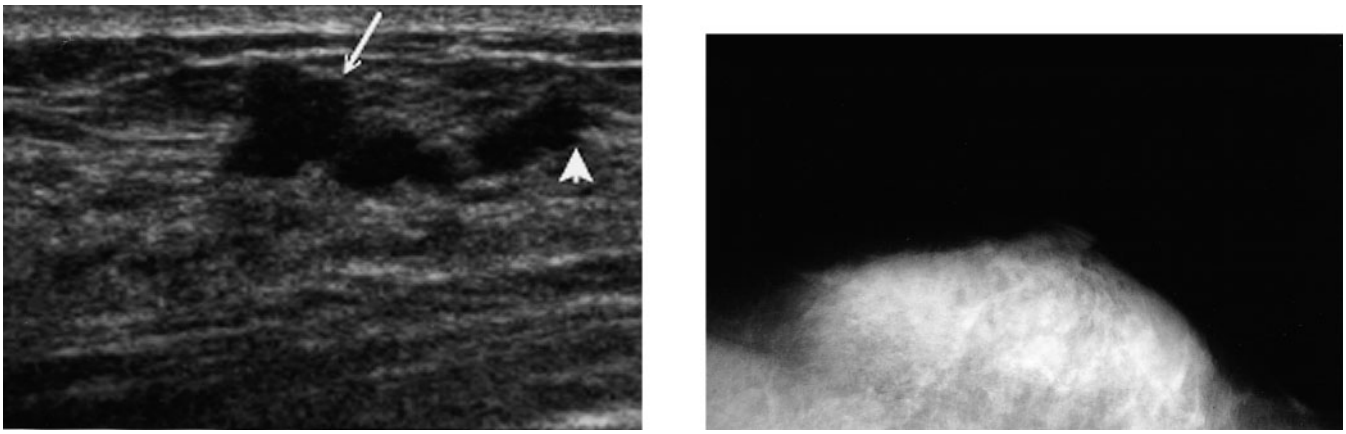
The Student's *t*-test was used for the comparison of age, AP/W ratio and vessel number. Chi-square test was used for the single ultrasound tumour features and multiple logistic regression analysis was used for modelling the combination of features. A dichotomization of the tumour descriptors into benign and malignant features was performed. Sensitivity, specificity, positive predictive value, negative predictive values and accuracy were calculated for calcification detection, which was compared with the findings of X-ray mammography.

Results

Of the 488 cases of invasive ductal carcinomas and 65 cases of intraductal carcinomas, the histology of invasive carcinomas included infiltrating ductal carcinoma (82.1%), invasive lobular carcinoma (7.2%) and others. The invasive carcinomas with extensive intraductal component (EIC) or adjacent intraductal carcinoma were classified as invasive carcinoma. The histology of the intraductal carcinomas included 42 comedo type ductal carcinoma *in situ*, 11 cribriform type, 6 solid type, 4 papillary carcinomas and 2 others. The median age for invasive and intraductal carcinoma was 47 years and 48 years, respectively. The mean size with standard deviation of the invasive and intraductal carcinomas were 2.7 ± 1.9 cm and 2.4 ± 1.4 cm, respectively ($p=0.196$). The accuracy rate of ultrasound diagnosis was 92.1% for invasive carcinoma (92.7%, 90.0% and 86.4% for invasive ductal carcinoma, invasive lobular and others, respectively). The accuracy for intraductal carcinoma was 84.8%, and for comedo type and non-comedo type, 88.5% and 80%, respectively. The ultrasound characteristics of invasive and intraductal carcinoma are shown in Table 1. An oval or lobulated shape was found more frequently in intraductal carcinoma than in invasive carcinomas (36.9% and 23.8%, respectively, $p=0.022$) (Figure 1). The percentage of tumours with isoechoic internal echogenicity, uniform echotexture, neutral acoustic transmission and bilateral edge shadowing were found to be significantly lower in invasive carcinomas than in intraductal carcinomas with odds ratio of 0.3, 0.4, 0.5 and 0.5, respectively. The invasive carcinomas had more feeding vessels than intraductal carcinomas, with mean vessel number of 2.2 and 1.6, respectively ($p=0.021$). Multiple logistic regressions in a stepwise model of the significant parameters was used to select the independent indicators and the results are shown in Table 2. The internal echogenicity was the only significant differentiating factor. The intraductal carcinomas show a higher percentage of isoechoic internal echogenicity (odds ratio of 2.2) than invasive carcinoma ($p=0.042$). The ultrasound features in comedo and non-comedo type intraductal carcinomas are shown in Table 3. The comedo type intraductal carcinoma had a significantly higher percentage of irregular shape on ultrasound than non-comedo type (73.8% *vs* 43.5%, respectively). Calcifications demonstrated

Table 1. Ultrasound features of invasive and intraductal carcinomas

Features	Invasive carcinoma ($n=488$)	Intraductal carcinoma ($n=65$)	Odds	Odds ratio	*p*-value
Shape					
oval/lobulated	116 (23.8%)	24 (36.9%)	0.21	1.0	
irregular	372 (76.2%)	41 (63.1%)	0.11	0.5	0.022
Margin					
smooth	79 (16.2%)	13 (20.0%)	0.16	1.0	
irregular	409 (83.8%)	52 (80.0%)	0.13	0.8	0.438
Internal echogenicity					
isoechoic	133 (27.3%)	35 (53.8%)	0.26	1.0	
hypoechoic	355 (72.7%)	30 (46.2%)	0.08	0.3	<0.001
Internal echo texture					
uniform	83 (17.0%)	18 (27.7%)	0.22	1.0	
non-uniform	405 (83.0%)	47 (72.3%)	0.12	0.5	0.036
Acoustic transmission					
neutral	192 (39.3%)	39 (60.0%)	0.20	1.0	
shadowing	296 (60.7%)	26 (40.0%)	0.09	0.4	0.002
Bilateral edge shadowing					
yes	34 (7.0%)	13 (20.0%)	0.38	1.0	
no	454 (93.0%)	52 (80.0%)	0.11	0.3	<0.001
AP/W ratio					
$\leqslant 0.7$	290 (59.4%)	44 (67.7%)	0.15	1.0	
>0.7	198 (40.6%)	21 (32.3%)	0.11	0.7	0.201



(a) (b)

Figure 1. Papillary intraductal carcinoma in a 55-year-old woman with a subtle nodule in the left breast clinically. (a) Radial view of ultrasound shows lobulated (arrow), mildly hypoechoic mass with intraductal extension (arrow head) and no acoustic shadowing. (b) Mammogram shows dense breast parenchyma without obvious abnormality.

Table 2. Multiple logistic regression analysis of ultrasound features of invasive and intraductal carcinomas

Findings	Odds ratio	95% Confidence interval (lower–upper)	*p*-value
Bilateral edge shadowing	2.4	0.9638–5.9519	0.060
Acoustic transmission	0.5	0.7841–3.2111	0.232
Isoechoic internal echogenicity	2.2	1.0281–4.8847	0.042
Irregular shape	0.8	0.3952–1.7937	0.056

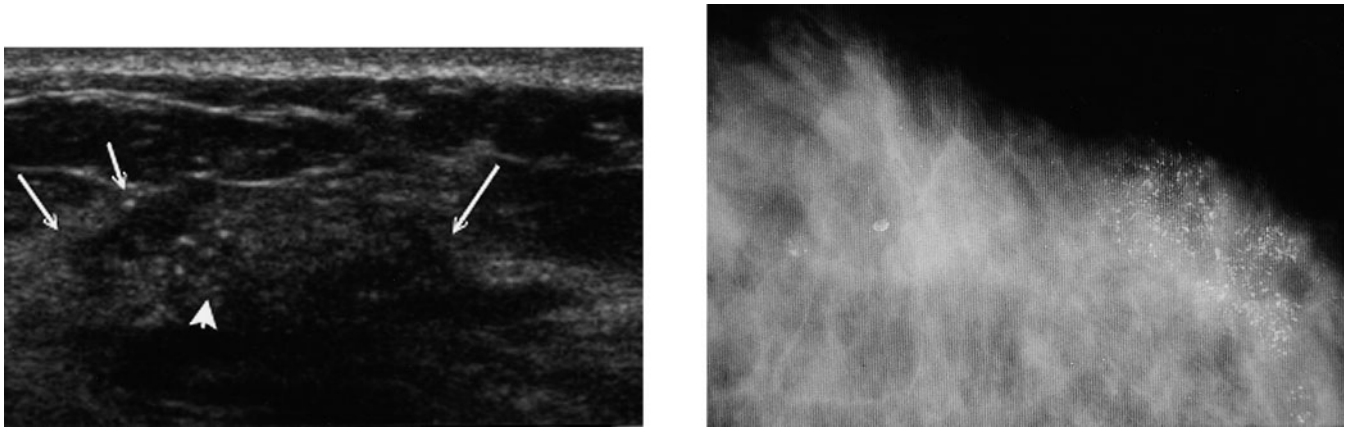
by X-ray mammography were found more frequently in comedo type intraductal carcinoma than in invasive carcinoma (69.2% *vs* 41.5%, respectively) (Figure 2), and only 35% of non-comedo type intraductal carcinoma showed calcifications. The presence of calcifications on ultrasound was confirmed by X-ray mammography. The sensitivity, specificity and accuracy of calcification detection by ultrasound in comedo, non-comedo type intraductal carcinomas and invasive carcinomas are stated in Table 4. The positive predictive value of calcifications detected by ultrasound for invasive, comedo type and non-comedo type intraductal carcinoma were 53.8%, 83.3%, and 60%; the accuracy rates were 63.2%, 63.6% and 64%, respectively.

Discussion

Breast ultrasound is considered mandatory in the evaluation of the mammographically dense breast in all ages [12]. The accuracy rate of ultrasound for palpable breast tumours has been reported as high as 95% with an experienced operator [13], and has also been recommended as the best imaging method for palpable breast lesions in

Table 3. Ultrasound features of comedo and non-comedo intraductal carcinomas

Features	Comedo (n=42)	Non-comedo (n=23)	Odds	Odds ratio	*p*-value
Shape					
oval/lobulated	11 (26.2%)	13 (56.5%)	1.18	1.0	
irregular	31 (73.8%)	10 (43.5%)	0.32	0.3	0.030
Margin					
smooth	7 (16.7%)	6 (26.1%)	0.86	1.0	
irregular	35 (83.3%)	17 (73.9%)	0.49	0.6	0.518
Internal echogenicity					
isoechoic	21 (50.0%)	14 (60.9%)	0.67	1.0	
hypoechoic	21 (50.0%)	9 (39.1%)	0.43	0.6	0.401
Internal echo texture					
uniform	12 (28.6%)	6 (26.1%)	0.50	1.0	
non-uniform	30 (71.4%)	17 (73.6%)	0.57	1.1	0.831
Posterior acoustic transmission					
neutral	27 (64.3%)	12 (52.2%)	0.44	1.0	
shadowing	15 (35.7%)	11 (47.8%)	0.73	1.7	0.341
Bilateral edge showing					
yes	9 (21.4%)	4 (17.4%)	0.44	1.0	
no	33 (78.6%)	19 (82.6%)	0.58	1.3	0.758
AP/W ratio					
$\leqslant 0.7$	27 (64.3%)	17 (73.9%)	0.63	1.0	
>0.7	15 (35.7%)	6 (26.1%)	0.40	0.6	0.427



(a) (b)

Figure 2. Comedo-type intraductal carcinoma in a 49-year-old woman with a palpable lump in the left breast. (a) Radial view of ultrasound shows lobulated (arrows), isoechoic mass with clustered calcifications (arrow head). (b) Mammogram shows a cluster of pleomorphic microcalcifications.

young women [5]. The prevalence of breast cancer in Taiwan is only a quarter that of Western nations [3], the median age was reported as 47 years old, which is 8 years younger than reported in Western women. Ultrasound is an important examination tool in the dense breasts and the diagnostic accuracy rate in some studies was higher than that of X-ray mammography [4, 14]. Ultrasound, however, has not been considered an acceptable screening modality because of the poor detection of microcalcifications, an important feature of intraductal carcinomas on X-ray mammography [7].

The ultrasound features of invasive carcinomas include irregular shape, irregular margin, internal hypoechogenicity, non-uniform distribution of internal echotexture, shadowing of acoustic transmission, loss of bilateral edge shadowing and calcifications in hypoechoic lesions [8, 15]. The ultrasound appearance of intraductal carcinomas may indude hypoechoic masses, dilated ducts with peripheral extension or microcalcifications [16]. In this study, most of the intraductal carcinomas were non-screening detected and usually presented as palpable masses or subtle nodules clinically. The non-screening detected intraductal carcinomas showed the same malignant ultrasound features as the invasive carcinomas except that intraductal carcinomas showed a higher proportion of oval or lobulated shape, isoechoic internal echogenicity, uniform echotexture, bilateral edge shadowing and neutral acoustic transmission than invasive carcinomas. Irregular shape in breast ultrasound has been reported as the most reliable indicator of malignancy [13, 17]. In this study, irregular shape was found more frequently in the invasive carcinomas with an odds ratio of 2.0.

Two-thirds of the invasive carcinomas were markedly hypoechoic in this study and less than 50% of the intraductal carcinomas were hypoechoic. Therefore, echogenicity is a useful parameter in differentiating intraductal from invasive carcinomas and it was the only significant factor in multivariate analysis. Although there is no standard definition of a hypoechoic lesion and a lack of uniformity among the observers, intraductal carcinoma, especially the non-comedo type, usually presents itself as isoechoic lesion because these lesions tend to be low grade and show less cell necrosis and calcifications. Shadowing of acoustic transmission is the result of attenuation of the sound beam by the desmoplastic reaction to breast cancer [18]. Usually, intraductal carcinoma shows less desmoplastic reaction, which explains why only 40% of intraductal carcinomas demonstrated posterior shadowing in comparison with 60% of invasive carcinomas.

Bilateral edge shadowing is caused by a reduction of reflection echoes by diffraction of the sound waves that touch the margin of a round boundary [19], and is regarded as a criterion of benign lesions. In this study, edge shadowing was found in 20% of intraductal carcinomas, significantly higher than in the invasive ones. Leucht et al reported only two carcinomas that presented edge shadowing, and the pathology revealed medullary and colloid carcinomas [20].

The AP/W ratio was a useful criterion to differentiate benign tumours from malignant tumours [13]. Both intraductal and invasive carcinomas grow in all directions, in contrast to the slowly growing fibroadenoma that keeps a flatter shape within normal tissue planes. Thus, AP/W ratio was not a good parameter for differentiating intraductal carcinoma from invasive carcinoma. Colour Doppler ultrasound was an adjunct to ultrasound in the differential diagnosis of breast lesions [21], and malignant tumours were characterized by hypervascularity with more

Table 4. Detection of microcalcifications in invasive and intraductal carcinomas by ultrasound

	Invasive carcinoma (n=488)	Intraductal carcinoma	
		Comedo (n=42)	Non-comedo (n=23)
Calcifications shown in			
Mammography	41.5%	69.2%	35.0%
Sonography[a]			
Sensitivity	65.1%	62.5%	30.0%
Specificity	61.9%	66.7%	86.7%
PPV	53.8%	83.3%	60.0%
NPV	72.2%	40.0%	65.0%
Accuracy rate	63.2%	63.6%	64.0%

[a]Calcifications in mammogram as the standard.
PPV, positive predictive value; NPV, negative predictive value.

than one vascular pole [22]. Invasive carcinomas have more feeding vessels than the intraductal carcinomas, 2.2 and 1.6 vessels, respectively, in this study.

In the limited number of cases of intraductal carcinoma, shape was found as the only significant differentiating factor between comedo and non-comedo type in this study. Comedo type intraductal carcinoma is usually associated with higher histological grade, mitotic count and tendency to have more frequency of intraductal spread which results in a higher percentage with an irregular shape.

Although ultrasound is less sensitive than mammography in the demonstration of microcalcifications [23], other authors have detected the majority of calcifications with a high frequency probe [24, 25]. Most malignant tumours were hypoechoic allowing calcifications to be easily demonstrated by ultrasound as bright spots within hypoechoic nodules [24]. Calcifications were more frequently demonstrated in comedo type intraductal carcinoma than in invasive carcinoma or non-comedo type intraductal carcinoma in this study. There was no difference in the demonstration of calcifications by ultrasound between invasive and intraductal carcinomas (63% *vs* 64%), even though the invasive carcinomas presented more frequently as hypoechoic masses. In this study, most of the intraductal carcinomas were symptomatic. Whether ultrasound could have the same ability to detect microcalcifications in the screening setting or in asymptomatic intraductal carcinoma needs further study. Evans et al found no substantial differences in the proportion of masses, architectural distribution and morphology of calcifications in symptomatic and screening detected intraductal carcinomas [26].

In conclusion, the accuracy of ultrasound diagnosis of non-screening detected intraductal carcinomas was the same as that for invasive carcinoma in this population. Sonographically, isoechoic internal echogenicity was more frequently seen in intraductal carcinomas. Irregular shape and calcifications were found more frequently in comedo type intraductal carcinoma in comparison with non-comedo type. About 60% of microcalcifications in intraductal or invasive carcinomas were demonstrated by ultrasound. Ultrasound may play an adjunctive role in detecting asymptomatic breast cancer in the future.

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