category in both men and women; more women were LTCI-certified than men. Among participants aged 85 years or older, about 34% of men and 51% of women were LTCI-certified.

DISCUSSION

To characterize the study population, we compared selected health-related characteristics of the population with those of the Japanese general population, by sex and age, using data from The National Health and Nutrition Survey in Japan, 2005.[26] Among men, the proportion of current smokers was higher in the study population than in the general population. The proportions of current smokers at baseline in the present cohort population by age category were 56.7% to 59.5%, 46.8% to 50.6%, 31.4% to 40.4%, and 21.3% to 25.9% for men in their 40s, 50s, 60s, and 70s, respectively (Table 2); the corresponding figures from the national survey were 44.1%, 42.5%, 34.0%, and 20.0% (≥70 years). In contrast, smoking status among women in the study population was very similar to that in the general population. Other variables, including obesity, underweight, history of serious diseases, alcohol drinking, and time spent walking, were similarly prevalent among middle-aged and elderly men and women in the study population and general population. To take one example, the proportions of men who were obese (BMI of ≥25.0) at baseline in the present cohort population by age category were 33.8% to 35.1%, 34.7%, 30.8% to 32.1%, and 26.3% to 29.1% for those in their 40s, 50s, 60s, and 70s, respectively (Table 2); the corresponding figures from the national survey were 34.1%, 31.4%, 30.7%, and 26.0% (≥70 years), respectively.

We also compared the LTCI certification status of the participants with that of the Japanese population by sex and age.[27] The proportions of those certified at baseline in the present cohort population, by age category, were 2.4%, 4.5%, 7.4%, 15.0%, and 34.2% for men aged 65–69, 70–74, 75–79, 80–84, and ≥85 years (Table 4); the corresponding figures from the estimated national survey were 3.0%, 6.2%, 11.9%, 22.1%, and 45.0%, respectively.[27] The same comparison among women yielded similar results, with smaller proportions in the present cohort population. These observed smaller proportions were not unexpected, because people with disabilities have more difficulties in responding to questionnaires. However, the small magnitude of the difference indicates that the selection bias was not serious.

Our study had some limitations. First, the response rate (64.2%) was not very high. The response rates of men and women aged 40 to 64 years were lower (54.9% and 60.4%, respectively) than those of men and women aged 65 years or older (76.2% and 72.4%, respectively). These relatively low response rates, especially among participants aged 40 to 64 years, should be kept in mind when interpreting the study results. Second, among the psychosocial variables studied, the items regarding job status and educational status, social support, and participation in community activities have not been adequately validated. Third, LTCI certification does not directly indicate an individual's disability status; however, it does reflect the burden of disability on society.[15,16]

We have already conducted a prospective cohort study in the catchment area of Ohsaki Public Health Center. This study began in 1995 and was named the Ohsaki National Health Insurance (NHI) beneficiary's Cohort Study, or the Ohsaki Cohort Study.[5] The primary purpose of that study was to demonstrate quantitatively the economic impact of health-related lifestyles; the Ohsaki Cohort 2006 Study, in contrast, does not assess medical costs. The catchment area of the Ohsaki Public Health Center included Furukawa City, and the towns of Nakaniida, Onoda, Miyazaki, Shikama, Matsuyama, Sanbongi, Kashimadai, Iwadeyama, Naruko, Wakuya, Tajiri, Kogota, and Nango. Among these areas, the city of Furukawa, and the towns of Matsuyama, Sanbongi, Kashimadai, Iwadeyama, Naruko, and Tajiri were consolidated to form the city of Ohsaki on 31 March 2006. The population of the present study and that investigated in the Ohsaki Cohort overlap by about one-third.

In conclusion, we have begun a large population-based prospective study that focuses on psychosocial factors and LTCI certification status. The psychological factors include measurements of job status and educational status, psychological distress,[20–23] social support,[24] participation in community activities, and the Kihon Checklist.[25] LCTI certification is followed up as an alternative to individual disability status, and as a measure of the economic burden of disability on society.

ACKNOWLEDGEMENTS

This study was supported by Health Sciences Research Grants (H19-Seisaku-Ippan-026, H18-Choju-Ippan-014, H21-Choju-Ippan-001) from the Japanese Ministry of Health, Labour and Welfare, and a Grant-in-Aid for Scientific Research (B) (21390200) from the Japan Society for the Promotion of Science.

The authors thank Yoshiko Nakata, Mika Wagatsuma, Naoko Sato, and Yuki Takeda for their technical assistance.

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Dose-escalation phase I study in metastatic breast cancer patients with combination of paclitaxel and tegafur·uracil

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Received April 24, 2009; Accepted August 7, 2009

DOI: 10.3892/ol_00000008

Abstract. The study present the results of the dose-setting study of concomitant weekly administration of paclitaxel and tegafur·uracil (UFT) for metastatic breast cancer. Eligible patients who entered the study underwent two or more courses of weekly paclitaxel + UFT therapy as the protocol therapy. The initial dose (level 1) was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day. At level 2, paclitaxel remained the same, but UFT was increased to 600 mg/day. At level 3, only paclitaxel was increased to 90 mg/m^2. Twelve patients were enrolled in this study between September 2000 and September 2002. Three patients were assigned to level 1. Grade 3 liver dysfunction (increased aspartate aminotransferase and alanine aminotransferase) was noted in one patient and grade 4 neutropenia was noted in one patient, showing that dose-limiting toxicity was detected in 2/3 patients. In accordance with the protocol, UFT was fixed at 400 mg/day and paclitaxel was decreased to 60 mg/m^2 at level -1, and then increased to 70 mg/m^2 at level 0. The overall effective rate after completion of two courses was 33% (3/9) including one case of complete response and two cases of partial responses. The remaining patients presented with stable diseases and no patient had progressive disease. In this study, weekly paclitaxel with concomitant UFT was administered. The recommended doses of paclitaxel and UFT were determined to be 70 mg/m^2 and 400 mg/day, respectively. As the toxicity profile shows, the highest toxicity level of this regimen was neutropenia and liver dysfunction, and dose-limiting toxicity was neutropenia.

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Key words: uracil and tegafur, paclitaxel, phase I, metastatic breast cancer

Introduction

An anthracycline-containing regimen represents the first-line palliative chemotherapy (1-3). However, it is necessary to develop non-anthracycline combination regimens to provide salvage therapy in metastatic breast cancer patients who have relapsed during or after anthracycline-containing combinations. Although new salvage chemotherapy using (or in combination with) novel anticancer drugs has been studied (4-6), survival benefits and higher response rates are often countered by increased toxicity and complexity of regimen. An effective combination chemotherapy regimen that is both simple and has lesser toxicity would be valuable.

Paclitaxel is highly effective for both breast cancer without previous treatment (7) and breast cancer previously treated with anthracycline (8). Findings in a Japanese late phase II study showed the effective rate in metastatic breast cancer patients to be 33.7% (21/62) (9). Clinical evaluation of weekly regimens was frequently performed. Higher effects with mild adverse events compared to those of the approved dosage/application method, comprising an every-three-week regimen, have also been reported (10). These regimens can be administered on an outpatient basis, which is an advantage.

5-Fluorouracil is used in combination with anthracycline anticancer drugs and cyclophosphamide for the treatment of breast cancer and is administered by bolus injection in many cases. However, continuous intravenous infusion is the best administration method because the effect of 5-fluorouracil is time-dependent and increases with the duration of exposure of tumor cells (11). Several reports have shown that continuous intravenous infusion was effective for colon carcinoma.

Thus, we paid attention to tegafur·uracil (UFT) because its oral administration obtains area under the curve comparable to that obtained by continuous intravenous infusion of 5-fluorouracil. UFT is an anticancer drug developed in Japan and consists

of the masked compound of 5-fluorouracil (tegafur) and uracil. UFT inhibits the rate-limiting decomposition enzymes of 5-fluorouracil that is dihydropyrimidine dehydrogenase (DPD). UFT has tegafur and uracil at a molar ratio of 1:4. The effects of UFT alone on local progressive and metastatic breast cancer were reported to be 32 (12) and 39% (13), respectively.

This study presents the results of the dose-setting study of concomitant weekly administration of paclitaxel and UFT for metastatic breast cancer.

Patients and methods

The eligibility criterion of this study was the presence of a measurable or evaluable lesion. Other criteria included: a two-week or longer drug withdrawal after previous therapy, adequate bone marrow function, liver function and renal function, 75-year-old or younger age, an expected survival of 3 months or longer, performance status 0-2 and the absence of active double cancer. Informed consent was obtained in writing from the patients enrolled in the study.

Eligible patients who entered the study underwent 2 or more courses of weekly paclitaxel + UFT therapy as the protocol therapy. One course of this regimen took 4 weeks. Paclitaxel was infused intravenously for 60 min on days 1, 8 and 15, and UFT was orally administered daily for 21 days, followed by drug withdrawal for 1 week. As premedication for hypersensitive reactions, dexamethasone 20 mg d.i.v., diphenhydramine 500 mg p.o. and ranitidine 50 mg i.v. were administered 30 min before paclitaxel administration.

The dose escalation schedule was set as: the initial dose (level 1) was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day. At level 2, paclitaxel remained the same, but UFT was increased to 600 mg/day. At level 3, only paclitaxel was increased to 90 mg/m^2. When the initial dose was determined to be the maximum tolerated dose (MTD), level 0 and level -1 were set as follows: at level 0 and level -1, the dose of UFT was fixed at 400 mg/day and paclitaxel was changed to 70 mg/m^2 at level 0 and 60 mg/m^2 at level -1 (Table I). Dose-limiting toxicity (DLT) was defined in accordance with the National Cancer Institute Common Toxicity Criteria. The criteria were: grade 4 thrombocytopenia, grade 3 pyrexial neutropenia (≥38°C), grade 4 neutropenia that persists for ≥4 days, grade 3-4 peripheral neuropathy and grade 3-4 non-hematological toxicity (excluding depilation, nausea and vomiting). One dose level was assigned to a cohort of 3 patients and when no DLT was noted, the study proceeded to the next dose level. When DLT was noted in 1/3, 3 additional patients were assigned to the same level. When DLT was noted in ≥2 patients at the same dose level, the dose was determined to be MTD. A one-level lower dose than MTD was selected as the recommended dose (RD) for the phase II study.

Table I. Dose escalation scheme.

Dose level	Paclitaxel (mg/m^2)	UFT (mg/body)
-1	60	400
0	70	400
1	80	400
2	80	600
3	90	600

Table II. Patient characteristics.

Characteristics	No. of patients	%
No. of patients entered	12	
Age, year		
Median	53	
Range	40-73	
Performance status		
0	10	83.3
1	2	16.7
2	0	0.0
Menopausal status		
Pre-	3	25.0
Post-	9	75.0
No. of metastatic sites involved		
1	8	66.7
2	4	33.3
Hormone receptor status		
Estrogen or progesterone		
Positive receptor	7	58.3
Negative receptor	5	41.7
Unknown	0	0.0
Prior chemotherapy		
Prior adjuvant chemotherapy	9	75.0
Prior chemotherapy for metastatic disease	8	66.7
Prior anthracycline	10	83.3
Prior taxane	4	33.3

Table III. Toxicity according to dosing level.

Level	PTX/UFT	No. of patients	DLT	No. of patients with DLT
-1	60/400	5	-	0
0	70/400	4	-	0
1	80/400	3	Liver dysfunction, neutropenia	2

PTX, paclitaxel; DLT, dose-limiting toxicity; UFT, uracil and tegafur.

Table IV. Toxicity profiles.

	Grade									
	0		1		2		3		4	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%
Leukocytopenia	7	64	1	9	1	9	2	18	-	
Neutropenia	7	64	1	9	1	9	-		2	18
Thrombocytopenia	11	100	-		-		-		-	
Fever	11	100	-		-		-		-	
Diarrhea	11	100	-		-		-		-	
Alopecia	-		7	64	4	36	-		-	
Neurosensory	6	55	5	45	-		-		-	
Skin	11	100	-		-		-		-	
Stomatitis	10	91	1	9	-		-		-	
Arthralgia	10	91	1	9	-		-		-	
Myalgia	11	100	-		-		-		-	
Liver dysfunction	10	91	-		-		-		1	9
Hypersensitivity reaction	10	91	-		1	9	-		-	
Fatigue	9	82	2	18	-		-		-	
Appetite loss	9	82	2	18	-		-		-	
Nausea	9	82	2	18	-		-		-	
Headache	9	82	2	18	-		-		-	
Flushing	8	73	3	27	-		-		-	

Results

Twelve patients were enrolled in this study between September 2000 and September 2002. The median age of the patients was 52.8 years of age (42-67 years) and the performance status (ECOG) was 0 in the 12 patients (Table II). Eleven patients had metastatic breast cancer and 1 patient had local progressive breast cancer. Patients with metastatic breast cancer had previously undergone chemotherapy and 6 of them were on chemotherapy including anthracycline.

Three patients were assigned to level 1. Grade 3 liver dysfunction (increased apartate aminotransferase and alanine aminotransferase) was noted in 1 patient and grade 4 neutropenia was noted in 1 patient, showing that DLT was detected in 2/3 patients. In accordance with the protocol, UFT was fixed at 400 mg/day and paclitaxel was decreased to 60 mg/m^2 at level -1 and then increased to 70 mg/m^2 at level 0.

Five patients were assigned to level -1, and 2 of the patients were handled as dropouts. One dropout developed grade 3 neutropenia in the first course and postponed administration of the drugs. Recovery, however, was delayed and the protocol therapy was discontinued. The safety evaluation committee advised the addition of 1 patient to confirm safety and 1 patient was thus added. However, the fourth patient was also judged as a dropout, since hypersensitive reaction developed immediately after initial administration of paclitaxel. Thus, 5 patients were enrolled. No DLT was noted in 3 patients judged evaluable and the study proceeded to the next step. At level 0 no DLT was noted in any patient. One patient was judged to be a dropout due to grade 4 neutropenia. However, persistence of neutropenia for 4 days or longer could not be confirmed (Table III). Based on these findings, MTD in this protocol was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day; RD was paclitaxel, 70 mg/m^2 and UFT, 400 mg/day.

Table V. Overall tumor response.

Tumor response	Dose level		
	-1 (n=3)	0 (n=3)	1 (n=3)
CR	0	0	0
PR	0	2	1
SD	3	1	2
PD	0	0	0
CR+PR	0	2 (66.7%)	1 (33.3%)

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

Table IV shows the frequency of the main adverse events. DLT was neutropenia, but was complicated in 1 patient at level 1 and liver dysfunction occurred in 1 patient at level 1. The incidence of grade 3-4 neutropenia was 18%.

Non-hematological drug-related toxicities were rarely severe and remained easily manageable except liver dysfunction, noted in 1 patient at level 1. Toxicities included alopecia (overall incidence 100%), neuropathy neurosensory (45%), stomatitis (9%), arthralgia (9%), fatigue (18%), appetite loss (18%), nausea (18%), headache (18%) and flushing (27%).

The overall effective rate after completion of 2 courses was 33% (3/9) including three cases of partial responses. The remaining patients presented with stable diseases (SD) and no patient had progressive disease. At dose levels, the effective rate at level 0, which was RD, was 66.7% (2/3) and continuity was also high (Table V). In continuous administration, partial responses were confirmed in some patients after 7 courses and complete response was confirmed in the remaining patients after 4 courses. Regarding the regional effects, the effect was noted in the liver, cervical lymph nodes and local skin.

Discussion

Our starting hypothesis is that administrating paclitaxel on a weekly basis not only improves the tolerability but in combination with oral UFT may also improve the anticancer effect. The results of our phase I trial, show both of these aspects. At the phase II recommended dose, the regimen was well tolerated and was associated with promising anticancer activity (14).

As chemotherapy for progressive/recurrent breast cancer, the current first choice is combination chemotherapy using multiple drugs, including anthracycline anticancer drugs. After taxan anticancer drugs were introduced, the efficacy of taxans for patients who became resistant to anthracyclines has been reported. Comparative studies, as well as studies on the combination of these anticancer drugs are underway.

Furthermore, weekly administration of paclitaxel in comparison with the standard every-three-week administration was recently investigated. Seidman *et al* performed a phase II clinical study of the weekly administration of paclitaxel in anthracycline-resistant breast cancer patients and obtained a high effective rate of 53% (10). Weekly administration was also reported in Japan, where adverse events (peripheral neuropathy and inhibition of the bone marrow) were milder and the effect was higher than those with every-three-week administration (15). According to Kimura *et al*, when 80 mg/m^2 paclitaxel was administered for 3 weeks followed by one-week withdrawal, a high effective rate of 71.4% was obtained (16).

5-Fluorouracil is included in combination regimens with cyclophosphamide, doxorubicin and 5-fluorouracil (CAF), as well as cyclophosphamide, epirubicin and 5-fluorouracil (CEF), and is administered intravenously. In contrast, oral 5-fluorouracil anticancer drugs are frequently administered in Japan. UFT is an oral anticancer drug consisting of tegafur and uracil. UFT inhibits the rate-limiting decomposition enzyme DPD, and is called dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine (DIF). The effective rate of UFT was found to be 32% (16/50) in a Japanese phase II study (10).

Basic investigations of the combination of paclitaxel and UFT using a lung-metastasized breast cancer model have been reported. The concomitant administration of the two drugs inhibited cancer growth without increasing toxicity. Thus, the duration of growth inhibition by paclitaxel alone was short (7-14 days) and re-growth occurred during the administration period, while the combination with UFT inhibited cancer growth for an extensive period of time. Repeated administration of paclitaxel has been reported to induce MDR and resistance, but 5-fluorouracil does not cross-react with MDR. Thus, the combination of paclitaxel and 5-fluorouracil is a useful one. In addition, DPD activity is higher in metastatic than in primary lesions, suggesting that a DIF UFT is an appropriate 5-fluorouracil anticancer drug in combination with paclitaxel.

In this study, weekly paclitaxel with concomitant UFT was administered. The recommended doses of paclitaxel and UFT were determined to be 70 mg/m^2 and 400 mg/day, respectively. As the toxicity profile shows, the major toxicity of this regimen was neutropenia and liver dysfunction, and DLT was neutropenia. Although hypersensitive reaction was noted after the initial administration of paclitaxel in 1 patient, no peripheral nerve toxicity attributable to paclitaxel occurred. This was a phase I study that aimed to determine the recommended dose. However, the number of patients enrolled was small and the effective rate at RD was 66.7% (2/3), suggesting the usefulness of this regimen.

Based on the results of this study, a phase II study is being performed at the recommended dose determined in the phase I study in patients previously treated with anthracycline. Results of this phase II study are anticipated.

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COMMENTS AND RESPONSES

Screening for Breast Cancer

TO THE EDITOR: In 2009, the U.S. Preventive Services Task Force (USPSTF) recommended that starting regular screening mammography before the age of 50 years should be an individual decision that takes patient context into account, including the patient's values regarding specific benefits and harms (1, 2). As a metric, Nelson and colleagues (3) calculated the number needed to invite (NNI) to screening to prevent 1 death from breast cancer by conducting a meta-analysis of several trials. They concluded that the net benefit is smaller for women aged 40 to 49 years with a larger NNI than for women aged 50 to 59 years. However, they did not consider different follow-up periods when comparing NNI by age group. For women aged 40 to 49 years, the average follow-up varied from 10.7 to 16.8 years in 8 trials included in the meta-analysis, whereas follow-up varied from 12.9 to 18.1 years for women aged 50 to 59 years in 5 trials and from 14.3 to 15.5 years for women aged 60 to 69 years in 2 trials. Shorter follow-ups for women aged 40 to 49 years will lead to lower cumulative mortality, which results in an overestimation of NNI.

We aimed to estimate the NNI adjusted by the follow-up period in each available study to compare NNIs between different age groups. We applied similar methods and included similar mammography trials to those used in Nelson and colleagues' meta-analysis (3). We conducted a meta-analysis of the trials to estimate the pooled relative risk (RR) from a random-effects model under a Bayesian analysis by using the WinBUGS package (MRC Biostatistics Unit, Cambridge, and Imperial College School of Medicine, London, United Kingdom) (4). We included 8 trials (5–10), 5 trials (5, 9, 10), 2 trials (5), and 1 trial (5) for women aged 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 to 74 years, respectively. The NNI to screening to prevent 1 breast cancer death was defined by the USPSTF as the inverse of the absolute risk reduction. Here, the risk was the mortality rate during follow-up (death per person). In considering the follow-up period of studies, we estimated NNI by using the mortality rate per year (death per person-year). The estimated NNI was based on a 1-year follow-up. Thus, when we compared the NNI on the assumption that the follow-up was x years, we divided the estimated NNI by x. We tried to estimate the NNIs on the assumption of 10-, 15-, and 20-year follow-ups.

The pooled RRs and NNIs for reducing breast cancer mortality in Nelson and colleagues' report and our estimates calculated by using the same condition are shown in the **Table**. Pooled RRs with adjustment for the follow-up were similar for all age groups. On the contrary, the NNIs differed depending on the assumed follow-up, that is, 10, 15, and 20 years. On the assumption of a 10-year follow-up, the estimated NNIs for women aged 40 to 49 and 50 to 59 years were 2399 (95% CI, 1195 to 8550) and 1708 (CI, 452 to 10 215), respectively. The longer the assumed follow-up, the smaller the estimated NNIs for all age groups. More important, the differences in NNIs between women aged 40 to 49 years and those aged 50 to 59 years were smaller in our analysis than in Nelson and colleagues' report.

When comparing NNIs, the follow-up period directly affects the results. The NNIs are necessarily greater in shorter follow-ups, which means that, if not adjusted for follow-up, the NNI can be overestimated for younger age groups with relatively shorter follow-ups. The USPSTF recommendations for mammography screening stated that an NNI of 1904 for women aged 40 to 49 years was too high, yet an NNI of 1339 for women aged 50 to 59 years was adequate (2). However, when we adjusted for the follow-up of the trials, the estimated NNIs for women aged 40 to 49 years were 1599 with a 15-year follow-up and 1199 with a 20-year follow-up. Whatever the conclusion, it should not be based on biased estimates of NNIs for reducing breast cancer mortality by age group.

Table. **Pooled RRs and NNIs for Breast Cancer Mortality From Mammography Screening Trials for All Ages***

Age	RR for Breast Cancer Mortality (95% CI)	NNI to Prevent 1 Breast Cancer Death (95% CI)
Reported value by USPSTF		
40–49 y	0.85 (0.75–0.96)	1904 (929–6378)
50–59 y	0.86 (0.75–0.99)	1339 (322–7455)
60–69 y	0.68 (0.54–0.87)	377 (230–1050)
70–74 y	1.12 (0.73–1.72)	NA
Our estimates under the same condition as USPSTF		
40–49 y	0.85 (0.75–0.96)	1908 (957–7339)
50–59 y	0.83 (0.69–0.99)	1229 (299–7490)
60–69 y	0.69 (0.54–0.87)	388 (64–4438)
70–74 y	1.2 (0.71–2.09)	NA
Adjusted by follow-up		
10-year follow-up		
40–49 y	0.85 (0.75–0.96)	2399 (1195–8550)
50–59 y	0.82 (0.69–0.98)	1708 (452–10 215)
60–69 y	0.68 (0.53–0.86)	520 (36–2907)
70–74 y	1.23 (0.71–2.14)	NA
15-year follow-up		
40–49 y	–	1599 (797–5700)
50–59 y	–	1139 (302–6810)
60–69 y	–	347 (24–1938)
70–74 y	–	NA
20-year follow-up		
40–49 y	–	1199 (598–4275)
50–59 y	–	854 (226–5107)
60–69 y	–	260 (18–1453)
70–74 y	–	NA

NA = not available; NNI = number needed to invite to screening; RR = relative risk; USPSTF = U.S. Preventive Services Task Force.
* Six trials, including the Canadian National Breast Screening Study-2, were used.

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Potential Conflicts of Interest: None disclosed.

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IN RESPONSE: We agree with Dr. Saika and colleagues that adjustment for follow-up time when estimating the NNI to mammography screening to prevent 1 breast cancer death provides more comparable results across age groups. However, the purpose of our meta-analysis was primarily to determine the effectiveness of mammography screening in reducing breast cancer mortality among women in their 40s, not to determine differences between age groups. Estimates of NNI are a way to illustrate magnitudes of effect that may be more relevant to clinical applications than RRs for some audiences. These estimates were calculated in the 2002 review (1), and we provided them in the updated review for consistency. Results indicate imprecise point estimates with overlapping confidence intervals that do not differentiate the 3 age groups in both the unadjusted NNI estimates and the estimates adjusted for follow-up provided by Dr. Saika and colleagues.

In general, NNI estimates would be expected to decrease with longer follow-ups for any event that accumulates over time, and Dr. Saika and colleagues results are consistent with this. However, their results are also a consequence of dividing the NNI estimates by the follow-up period, thereby imposing an inverse relationship by definition rather than allowing the data to reveal such a relationship. Their calculations also assume that the mortality rate is the same across all follow-ups, which may not be accurate, and for 20 years after screening, a period for which data are not yet available.

The USPSTF enlisted a more rigorous approach than using NNI estimates to evaluate ages to initiate and discontinue screening by commissioning statistical models from the Cancer Intervention and Surveillance Modeling Network (CISNET) (2). The USPSTF final recommendations (3) were based on its determination of the balance of benefits and harms of screening mammography for specific age groups from multiple data sources detailed in our evidence review and the CISNET report (2). Our NNI estimates were only 1 piece of this puzzle.

Also, to clarify, we included the Canadian National Breast Screening Study-2 (4) in our analysis of women age 50 to 59 years, although the reference in our review was incorrectly cited as the Canadian National Breast Screening Study-1.

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Potential Conflicts of Interest: None disclosed.

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The Need for Biomedically and Contextually Sound Care Plans in Complex Patients

TO THE EDITOR: Weiner and colleagues (1) provide evidence that error-free treatment plans are rarely created for patients with biomedical and contextual complexity (9%) and are not commonly created for those with contextual (22%) or biomedical (38%) complexity alone. This is not surprising given that primary care physicians are already expected to devote 1.5 times their available patient contact hours to providing preventive, long-term care, and acute medical services (2). Nonetheless, implementing improved skills in error-free or, at least, error-reduced care plans for the complex 1% to 5% of patients who use one quarter to one half of health resources (3) will be essential for patient-centered medical homes and accountable care organizations to succeed in augmenting quality care and lowering health-related costs (4). Barriers to improvement in these most needy patients, whose care is expensive, can be removed only through consistent identification and outcome-changing intervention, including contextual life-situation support.

Weiner and colleagues thus raise a practical, system-based question in this time of health reform: Can already overtaxed clinicians be expected to personally uncover and create individualized care plans in patients with biomedical and contextual complexity? Logically, to do so would require decreasing the number of patients per physician panel, thereby increasing available patient contact time; expanding the number of treatment-level clinicians (for example, physicians, physician assistants, nurse practitioners); or adding spe-

cialized support personnel to clinician teams, such as case managers (5), who can assist treating practitioners in individualizing biopsychosocial and health system support for complex patients.

As physicians intimately involved in augmenting the care of patients with health complexity, we see Weiner and colleagues' findings as a clinical challenge for physicians who wish to practice quality medicine. Perhaps a greater challenge, however, is for those involved in enhancing system-level care delivery (for example, in designing patient-centered medical homes or accountable care organizations) to create financially sustainable practice environments that allow practitioners time to consistently address biomedical and contextual needs in patients with complicated life and health situations.

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Potential Conflicts of Interest: The authors own a health complexity and physical and mental health integration medical management company.

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IN RESPONSE: A finding of our study that surprised us was that although physicians who spent more time with patients were more likely to probe for biomedical or contextual red flags, they were not more likely to provide contextually appropriate care. For example, in the case of a patient whose health literacy problems accounted for an inability to dose his diabetes medications correctly, physicians more often identified the literacy issue during longer visits but were not more likely to appropriately intervene. Physicians who intervened, however, did not on average have longer visits. Physicians who avoid contextual errors seem to think differently, considering context not as an afterthought but instead as a part of the clinical reasoning process. We recently studied an educational intervention that suggests such reasoning processes can be effectively taught (1).

Drs. Kathol and Kathol propose that if physicians had more time and specialized support personnel, such as case managers and midlevel providers, they would be more likely to provide contextually appropriate care. Although we did not find that additional time alone helped, the combination of additional time and a medical home environment might substantially improve care. Physicians who, during longer visits, unmasked health literacy problems as the root cause of a patient's poor diabetes control may simply have concluded that there was nothing they could do about it, without having, for instance, a diabetes educator who could assist. We share the concern that the major challenge for physicians involved in enhancing system-level care delivery is designing financially sustainable practice environments that support physicians who have developed the cognitive skills to individualize care, with the resources and tools needed to do so.

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Potential Conflicts of Interest: None disclosed.

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CORRECTION

Correction: Acute Sinusitis

In the recent In the Clinic on acute sinusitis (1), the figure title on page ITC3-2 was incorrect. The correct title is: "Diffuse pansinusitis with mucosal thickening and polyposis in the anterior sinuses." This has been corrected in the online version.

Reference

1. Wilson JF. In the clinic. Acute sinusitis. Ann Intern Med. 2010;153:ITC3-1-15. [PMID: 20820036]

Cancer Science
The official journal of the Japanese Cancer Association JCA

Comparison of core needle biopsy (CNB) and surgical specimens for accurate preoperative evaluation of ER, PgR and HER2 status of breast cancer patients

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(Received January 26, 2010/Revised May 8, 2010/Accepted May 18, 2010/Accepted manuscript online May 25, 2010/Article first published online June 15, 2010)

The roles of core needle biopsy (CNB) have become well established as an important preoperative diagnostic method for breast lesions. We examined the concordance of histological types, nuclear grades, hormone receptors, and human epidermal growth factor receptor 2 (HER2) status between CNB and surgical specimens in 353 cases. In addition, we analyzed the correlation between the number of CNB specimens obtained and accuracy of histological factors in order to explore the optimal number of CNB specimens. Between CNB and surgical specimens, concordance rates of histological type, nuclear grade, estrogen receptor (ER), and progesterone receptor (PgR) status (cut-off 0–<1%, 1–10%, and 10%<), and HER2 were 84.4%, 81.3%, 92.9%, and 89.3%, respectively. In 52 of 353 patients who were histopathologically diagnosed as ductal carcinoma *in situ* (DCIS) by CNB, final diagnosis was changed in to invasive ductal carcinoma (IDC) in surgical specimens. Statistically significant differences were detected in the discrepancy of the following factors between CNB and subsequent surgical specimens: histological types, nuclear grade, and PgR, between patients who received four or more cores and those who had received three or less cores. In addition, a similar tendency was also detected in estrogen receptor (ER) and HER2 as in the above, and the cases that received four cores reached to 100% concordance in diagnosis between CNB and surgical specimens. Therefore, the optimal numbers of CNB were considered four at least in assessing the histological type, invasion, nuclear grade, hormone receptor status, and HER2 status of individual patients in the preoperative setting. (*Cancer Sci* 2010; 101: 2074–2079)

The incidence of breast cancer is increasing worldwide, which is partly considered to be due to mass screening programs resulting in the discovery of clinically occult breast lesions.[1] In these lesions, relatively a more cautious approach is required to obtain appropriate tissue samples for preoperative pathological analysis. Roles of core needle biopsy (CNB) have become well established as an important diagnostic tool for both palpable and non-palpable breast lesions and it is considered the method of choice for tissue sampling.[2,3] In addition, CNB is less invasive than excision biopsy and generally provided more reliable information compared to fine needle aspiration biopsy cytology (FNAC), especially for providing architectural or histological information. For instance, an absolute sensitivity of ultrasound guided FNAC was 83.1% and that of CNB was 96.7%.[4] Accurate preoperative diagnosis of a breast lesion has recently considered essential for designing an optimal treatment algorithm in order to achieve a definite diagnosis without delay and with minimal biopsies.

The cases receiving preoperative systemic therapy have increased in order to reduce the tumor volume and eliminate possible micrometastasis for the patients with locally advanced breast carcinoma. Therefore, clinical demands on pathologists to provide not only histological diagnosis but also prognostic information for patients, including the determination of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) for treatment planning, have markedly increased for clinicians in institutions of many parts of the world.[2] The information obtained from CNB may be the only information available for determining the candidates for preoperative or neoadjuvant treatment.[2] However, the information obtained from CNB must reasonably reflect that in the whole tissue for determining a treatment strategy for these patients. Results of previous studies demonstrated that the concordance rate between CNB and surgical specimens were 61.7–99% for ER, 61.5–97.1% for PgR, and 80–96% for HER2, respectively.[1,2,5–7] However, it is also true that these studies evaluated only 100 cases at most with a limited statistical power to detect discordance, and results differed significantly between these studies.[5,6] Therefore, in this study, we examined the concordance rate of nuclear grades, hormone receptors, and HER2 status between CNB and surgical specimens in 353 Japanese patients with breast carcinoma.

There have been controversies as to the optimum number of the CNB specimens to be taken from the patients in order to obtain accurate information of whole carcinoma tissues. Three or four cores were initially recommended as the most appropriate or optimum number of the specimens in a pioneer stereotactic study, employing needles of different calibers and excursion.[8] Another study also demonstrated relatively a high correlation of histological parameters between CNB and surgical specimens with only two cores.[9] To the best of our knowledge, no studies have reported the correlation between the number of cores obtained and the status of hormone receptors and HER2 status in the whole specimens. Therefore in this study, we examined the correlation between the number of cores and the accuracy of histological types, nuclear grade, hormone receptors, and HER2 status, and attempted to establish the optimal number of cores taken from the patients in preoperative settings.

Materials and Methods

We examined 353 Japanese female patients with breast carcinoma without neoadjuvant chemotherapy who underwent CNB and surgical resection from January 2002 and June 2009 at the Department of Breast and Endocrine Surgery, Tohoku University Hospital in Sendai, Japan. We received informed consents from all the patients and the protocol for this study was

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doi: 10.1111/j.1349-7006.2010.01630.x

approved by the Ethics Committee at Tohoku University Graduate School of Medicine. The median age of the patients was 57 years (range, 27–85 years). All the core biopsies were performed under ultrasound guidance using a 16-gauge true-cut needle with an automated biopsy device.

We performed staining with hematoxylin–eosin (H&E) and immunohistochemicals for ER, PgR, and HER2 at the Department of Pathology, Tohoku University Hospital. After CNB and surgical resection of the primary tumors, the specimens were fixed in 10% formalin, embedded in paraffin, cut into 4-μm thick sections, and placed on the glue-coated glass slides. For determining the hormone receptor status, we employed the avidin–streptavidin immunoperoxidase method using the clone 6F11 antibody (Ventana, Tucson, AZ, USA) for ER and the clone 6 antibody (Ventana) for PgR in an automated immunostainer (Benchmark System; Ventana). A standardized immunohistochemistry kit (HercepTest for Immunoenzymatic Staining; Dako, Copenhagen, Denmark) was used for HER2 staining. Hematoxylin–eosin (H&E) and IHC staining were performed by a single and experienced technician. Positive controls for ER, PgR, and HER2 were breast carcinoma, whereas negative controls for immunostaining were hepatocellular carcinoma.

Two of the authors independently evaluated CNB samples and surgical specimens twice on different days. They were also blinded to the findings of CNB and surgical specimens, respectively. If there were discrepancies, they reached a final decision using evaluations from the third experienced pathologist. Olympus BX 50 and 20 X objectives (Tokyo, Japan) were used for the analysis. We examined the comparison between CNB samples and surgical specimens for the following parameters: histological types, nuclear grades, ER, PgR, HER2, correlation between the number of cores and status of hormone receptors, and HER2 status in operative specimens. Histopathological evaluations were based on World Health Organization (WHO) histological classification of tumors of the breast[10] and Rosen's Breast Pathology.[11] The nuclear grade was evaluated according to the Japan National Surgical Adjuvant Study of Breast Cancer (NSAS-BC) protocol.[12] By combining the nuclear atypia and mitotic counts, nuclear grades were defined as the summation of scores for the nuclear atypia (1 for low degree atypia; 2 for intermediate-degree atypia; 3 for high-degree atypia) with the scores for the mitotic counts per 10 high-power fields (×40 objective lens) (1 for 0–4 mitoses; 2 for 5–9 mitoses; 3 for 10 mitoses).[12] The nuclear grade was 1, 2, and 3 when the summation of scores for the nuclear atypia and those for mitotic counts were 2–3, 4, and 5–6, respectively.[12] Estrogen receptor (ER) and PgR were determined by nuclear staining graded from 0 to 8 using the Allred score.[13] The results were categorized as positive when the total score (TS), expressed as the sum of the proportion score (PS) and immunointensity score (IS),[13] was 3 or more.[13] In addition, we also evaluated the number of ER- and PgR-positive tumor cells according to the following criteria: cut-off 0–<1%, 1–10%, and 10%<, which was demonstrated by Arihiro *et al.*[14] We also defined the positive hormone receptor status as follows: cut-off 1%≤, discussed at the 11th St Gallen (Switzerland) expert consensus meeting on the primary treatment of early breast cancer in March 2009,[15] and cut-off 10%≤, defined by the J-score system.[14,16] In addition, with regard to HER2 evaluation of 225 cases excluding ductal carcinoma *in situ* (DCIS) diagnosed by CNB or surgical specimen, membranous staining was graded as the following: score 0–1+, 2+, and 3+.[2,6] A score of 0 was defined as no staining observed or membrane staining in <10% of tumor cells, and 1+ as faint/-barely perceptible membrane staining detected in more than 10% of the tumor cells.[2,17] Scoring of 2+ was assigned when there was weak to moderate complete membrane staining in >10% tumor cells; whereas 3+ consisted of uniform, intense membrane staining of >10% tumor cells.[2,17]

Statistical analysis, such as the one-factor ANOVA and simple regression analysis, were performed using StatMate III for Windows version 3.18 (ATMS, Tokyo, Japan). The agreement on the histological types, nuclear grade, hormone receptors, and HER2 status was tested using the kappa test.[18] Results obtained were considered significant at $P < 0.05$.

Results

Concordance of histological type between CNB samples and surgical specimens. The concordance rate of histological types between CNB and surgical specimens was 84.4% (298 of 353 cases) with a kappa value of 0.70 (Table 1). Concordance rates, defined as the number of CNB samples divided by surgical specimens of the following histological types, invasive ductal carcinoma (IDC), DCIS, invasive lobular carcinoma (ILC), and mucinous carcinoma, were as follows: 99.5% (196/197), 58.6% (75/128), 92.9% (13/14), and 100% (14/14), respectively (Table 1).

Concordance of nuclear grades. The concordance rate of nuclear atypia was 76.8% (271/353), including 41 cases with a score of 1, 191 cases with 2, and 39 cases with 3, with a kappa value of 0.55 (Table 2a). The concordance rate of mitotic counts was 82.2% (290/353), including 191 cases of with a score of 1, 57 cases with 2, and 42 cases with 3, with a kappa value of 0.69 (Table 2b). In addition, the concordance rate of nuclear grades was 81.3% (287/353), including 209 cases of with a score of 1, 38 cases with 2, and 40 cases with3, with a kappa value of 0.64 (Table 2c).

Comparison of ER and PgR status between CNB and surgical specimens. The agreement of ER status defined by the following criteria: cut-off 0–<1%, 1–10%, and 10%< was 92.9% (328/353), including 58 cases of cut-off 0–<1%, 12 cases of cut-off 1–10%, and 258 cases of cut-off 10%<, with a kappa value of 0.82 (Table 3a). The agreement of ER-positive or -negative status was as follows: 94.1% (332/353) for the Allred Score, 94.9% (335/353) for the proportion; cut-off level of 1%≤ and 96.0% (339/353) for the proportion; cut-off level of 10%≤, respectively. Sensitivity was 95.2% (279/293) for the Allred Score, 95.8% (277/289) for the cut-off level of 1%, and 96.8% (271/280) for the cut-off level of 10%≤, respectively. However, specificity was 88.3% (53/60) for the Allred Score, 90.6% (58/64) for the cut-off level of 1%≤, and 93.2% (68/73) for the cut-off level of 10%≤, respectively. In addition, positive predictive values (PPV) were 97.6% (279/286) for the Allred Score, 97.9% (277/283) for the cut-off level of 1%≤, and 98.2% (271/276) for the cut-off level of 10%≤, respectively.

The agreement of PgR status was 77.9% (275/353), including 105 cases of cut-off 0–<1%, 40 cases of cut-off 1–10%, and 125 cases of cut-off 10%<, with a kappa value of 0.66 (Table 3b). The concordance ratio of positive and negative was as follows: 86.1% (304/353) for the Allred Score, 89.5% (316/353) for the cut-off level of 1%≤, and 88.7% (313/353) for the cut-off level

Table 1. Analysis of the concordance of histological type between CNB and surgical specimens

		Surgical specimens			
		DCIS	IDC	ILC	Mucinous
CNB	DCIS	75	52	0	1
	IDC	0	196	1	0
	ILC	0	1	13	0
	Mucinous	0	0	0	14

CNB, core needle biopsy; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; mucinous, mucinous carcinoma.

Table 2. Analysis of the concordance of (a) nuclear atypia, (b) mitotic counts, and (c) nuclear grade between core needle biopsy (CNB) and surgical specimens

(a)

		Surgical specimens			
		Low	Intermediate	High	Total
CNB	Low	41	37	4	82
	Intermediate	11	191	26	228
	High	0	4	39	43
	Total	52	232	69	353

(b)

		Surgical specimens			
		Score 1	Score 2	Score 3	Total
CNB	Score 1	191	18	1	210
	Score 2	13	57	17	87
	Score 3	1	13	42	56
	Total	205	87	60	353

(c)

		Surgical specimens			
		Grade 1	Grade 2	Grade 3	Total
CNB	Grade 1	209	21	4	234
	Grade 2	12	38	20	70
	Grade 3	1	8	40	49
	Total	222	67	64	353

Table 3. Analysis of the concordance of (a) ER and (b) PgR between CNB and surgical specimens

(a) ER

		Surgical specimens			
		0–<1%	1–10%	10%<	Total
CNB	0–<1%	58	7	5	70
	1–10%	0	12	9	21
	10%<	0	4	258	262
	Total	58	23	272	353

(b) PgR

		Surgical specimens			
		0–<1%	1–10%	10%<	Total
CNB	0–<1%	106	21	5	132
	1–10%	0	40	23	63
	10%<	0	29	129	158
	Total	106	90	157	353

CNB, core needle biopsy; ER, estrogen receptor; PgR, progesterone receptor.

of 10%≤, respectively. Sensitivity was 84.6% (219/259) for the Allred Score, 88.7% (211/238) for the cut-off level of 1%≤, and 89.4% (185/207) for the cut-off level of 10%≤, respectively. However, specificity was 90.4% (85/94) for the Allred Score, 91.3% (105/115) for the cut-off level of 1%≤, and 87.7% (128/146) for the cut-off level of 10%≤, respectively. In addition, PPV were 96.1% (219/228) for the Allred Score, 95.5% (211/221) for the cut-off level of 1%≤, and 91.1% (185/203) for the cut-off level of 10%≤, respectively.

Concordance of HER2 status between CNB and surgical specimens. Agreement of the HER2 status defined by the following criteria: cut-off 0,1+, 2+, and 3+ was 89.3% (201/225 invasive carcinomas) including 182 cases of cut-off 0,1+, seven cases of cut-off 2+, and 12 cases of cut-off 3+, with a kappa value of 0.64 (Table 4).

Table 4. Analysis of the concordance of HER2 status between CNB and surgical specimens

		Surgical specimens			
		0–1+	2+	3+	Total
CNB	0–1+	182	6	0	188
	2+	4	7	10	21
	3+	0	4	12	16
	Total	186	17	22	225

CNB, core needle biopsy; HER2, human epidermal growth factor receptor 2.

Analyses of discordant cases. The discordance of histological types was 55 of 353 cases. Among 52 cases which were originally diagnosed as DCIS by CNB, and subsequently changed to IDC by surgical specimens, 63.5% (33 of 52) were T1mic and T1a. The discordance of nuclear grade, ER, PgR, and HER2 was 66 of 353, 25 of 353, 78 of 353, and 24 of 225 cases, respectively (Tables 1–4). We defined major discordance as the discordance of two grades or two scores, and minor discordance as the discordance of one grade or one score. Major discordance of nuclear grade, ER, and PgR accounted for 5 of 66, 5 of 25, and 5 of 78 cases, respectively (Tables 2,3). As for HER2 status, all of 24 discordant cases corresponded with minor discordance (Table 4). Some of these discordances were due to technical problems, for instance, there was only one core and insufficient sample volume caused difficulty in histopathological diagnoses. In the case of only one sampling core that was 100 μm in diameter with a very small amount of carcinoma tissue, accurate diagnosis was difficult. Five discordant cases of histological types, four major and two minor discordant cases of nuclear grades, three major and two minor discordant cases of ER and PgR, and two discordant cases of HER2 status were due to the technical problem described above. On the other hand, all of the other cases were due to intratumoral heterogeneity.

Correlation between the concordance rates and number of consecutive cores. One to five cores were obtained in clinical settings as follows: one core in 158 cases, two cores in 119 cases, three cores in 33 cases, four cores in 17 cases, and five cores in 26 cases. The concordance rate of histological types from one core to five cores was 82.3% (130/158), 83.2% (99/119), 84.8% (28/33), 88.2% (15/17), and 100% (26/26), respectively (Fig. 1a). The concordance rate of nuclear grades from one to five cores was 74.7% (118/158), 84.9% (101/119), 81.8% (27/33), 88.2% (15/17), and 100% (26/26) (Fig. 1b). The concordance rate of ER status was 91.1% (144/158) for one core, 95.8% (114/119) for two cores, 97.0% (32/33) for three cores, 100% (17/17) for four cores, and 100% (26/26) for five cores, respectively (Fig. 2a). The concordance rate of PgR was 88.6% (140/158) for one core, 87.4% (104/119) for two cores, 93.9% (31/33) for three cores, 100% (17/17) for four cores, and 100% (26/26) for five cores, respectively. In addition, the concordance rate of HER2 was 85.6% (83/97) for one core, 88.4% (61/69) for two cores, 91.3% (21/23) for three cores, 100% (15/15) for four cores, and 100% (21/21) for five cases, respectively (Fig. 2b). As for histological types, nuclear grades, and PgR, there were statistically significance between patients who received four or more cores and those who had received three or less cores ($P = 0.035$, $P = 0.012$, and $P = 0.020$, respectively). A similar tendency was also detected in ER and HER2 but did not reach statistical significance ($P = 0.087$ and $P = 0.053$, respectively).

doi: 10.1111/j.1349-7006.2010.01630.x

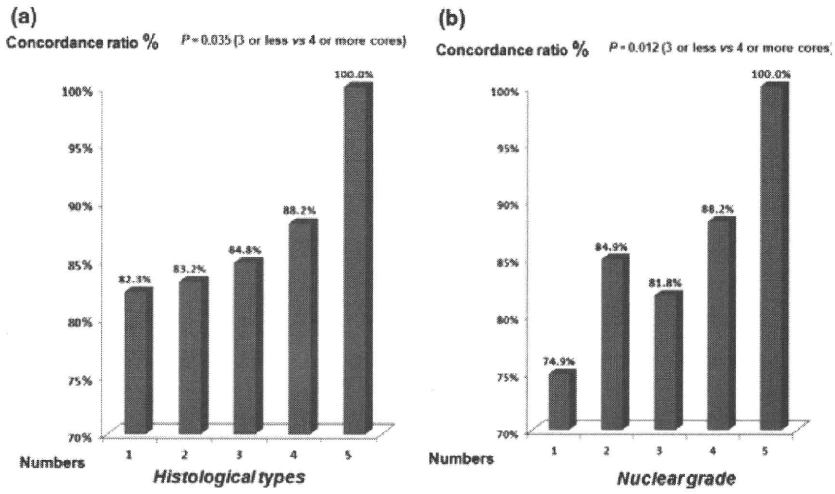

Fig. 1. Analysis of concordance rate of (a) histological type and (b) nuclear grade according to the number of core needle biopsies (CNB).

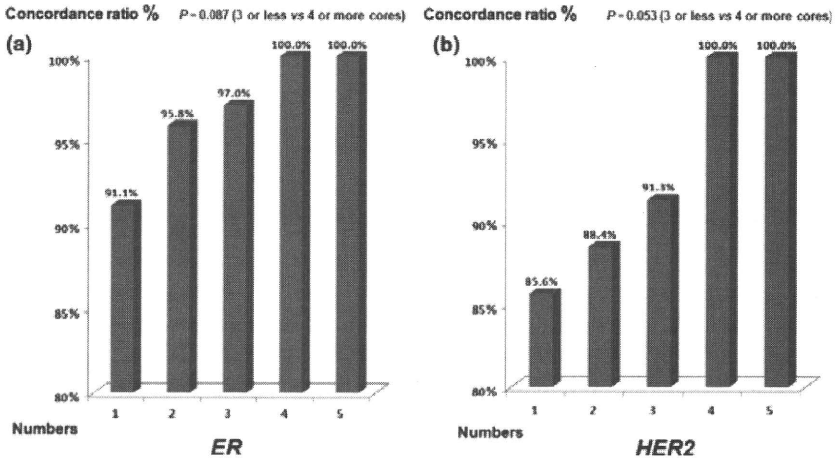

Fig. 2. Analysis of concordance rate of (a) estrogen receptor (ER) and (b) human epidermal growth factor receptor 2 (HER2) according to the number of core needle biopsies (CNB).

Discussion

Core needle biopsy (CNB) has been performed using a variety of devices to evaluate the nature of breast lesions. Core needle biopsy (CNB) has become the gold standard because of its lower inconclusive rate and the histological information it can provide.[19] The histological type of the lesions obtained by CNB was reported to be correlated closely with that of the excision specimen in 87 of 105 (83%) of cases.[5] In our present study, we demonstrated that the concordance rate of histological types between CNB and surgical specimens was 84.4% (298/353), which is very consistent with the results of report above. When the lesions are malignant, the presence or absence of invasion can be documented and the grade and type of tumor present can be assessed by histopathological evaluation of CNB.[19] It is also possible to examine ER, PgR, and HER2 status using immunohistochemistry in CNB specimens.[15] Therefore, information obtained from CNB greatly helps clinicians to determine a treatment plan for individual patients with regard to conservative management or primary chemotherapy.[19] However, some complications of CNB have been also reported in previous studies,[20–23] including postbiopsy pain,[20] hematoma,[21] infection[22] and seeding of carcinoma cells,[23] although such complications are considered rare if done in appropriate institutions by qualified staff. These indicate above all that CNB is a reliable and safe measure to diagnose breast disorders in a preoperative setting.

In our present study, 52 cases diagnosed as DCIS by CNB were subsequently diagnosed as IDC by surgical specimens; however, among these cases, 63.5% (33/52) were T1mic and T1a, and the tumor size was smaller than 2 cm. As for nuclear grades including nuclear atypia and mitotic counts, the concordance rates were almost 80%. In addition, more than 90% of discordant cases were within one grade discrepancies. In Table 2, we also demonstrate the tendency of nuclear atypia, mitotic counts, and nuclear grade of CNB to be lower compared to those of surgical specimens. This phenomenon is considered to be caused by the differences in methodologies employed between CNB and surgical specimens. We examined the higher atypical and mitotic area in surgical specimens, whereas we examined the narrow and limited area in CNB specimens. Therefore, the nuclear factors of surgical specimens tended to be worse than those of CNB. As for ER and PgR expression, results of previous studies demonstrated that the absolute concordance of ER and PgR between CNB and surgical specimens were 61.7–99% and 61.5–97.1%, respectively.[1,2,5–7] We demonstrated that the concordance rate of ER and PgR was 94.1–96.0% and 86.1–89.5%, respectively. The concordance of PgR was lower than that of ER, due to the fact that PgR immunoreactivity was weaker and more heterogenous than ER. We examined ER expression by Allred score and proportions of immunoreactive tumor cells were scored as follows: cut-off ≤1%[15] and 10%≤,[14,16] but there were no statistically significant differences. In addition, the concordance rate of HER2 status was 64–96%.[1,2,5–7] Recently, there have been increasing reports evaluating the use of HER2-targeted agents in neoadjuvant therapy for both primary operable and primary inoperable HER-positive breast cancer.[24,25] It is therefore important to achieve

a more definitive diagnosis of HER2 status in pre-operative CNB. We also demonstrated that there was discordance in judgments of ER, PgR, and HER2 between CNB specimens and surgically resected specimens in some cases. However, many of these discordant cases were detected more frequently in equivocal or borderline categories (Tables 3,4). In Table 4, it can be seen that four cases of HER2 score 2+ for CNB were changed to 1+ for surgical specimens, and four cases of CNB 3+ were changed to surgical 2+. We detected the strongest HER2 expression area in these tumors by CNB. Therefore, HER2 scores from surgical specimens were lower than those from CNB in these cases. We demonstrated that the disagreements were due to technical problems and intratumoral heterogeneity. If there were discrepancies between two evaluators, the evaluation of the third experienced pathologist was selected. In addition, histopathological staining was performed by a single and experienced technician. Two authors independently evaluated CNB samples and surgical specimens twice on different occasions. Therefore, these findings suggest that interobserver difference, different immunohistochemical technique, and different pre-analytical conditions were not the causes of discordance in the judgment of these factors. It is important for diagnostic accuracy to be established more definitively, and if possible, an increment of the number of CNB specimens may be considered more important because of intratumoral heterogeneity.

Several previous studies have tried to determine the optimum number of specimens to be obtained for ultra sound (US)-guided CNB to accurately diagnose histological subtypes.[26–29] One study demonstrated that among 73 lesions, cells indicating the diagnosis were present in the first specimen in 51 (70%), in the second specimen in 67 (92%), in the third specimen in 70 (96%), and in the fourth specimen in all 73 (100%) of cases.[27] This result suggested that a minimum of four specimens should be obtained with 14-gauge US-guided breast biopsy.[27] However, a study by Melotti *et al.*[29] examined the comparison of the quantity and quality of tissue harvested from breast biopsy when using 14-, 16-, and 18-gauge long-throw needles. The results in that study clearly demonstrated that when comparing 14-, 16-, and 18-gauge needles, accuracy rose with needles of increasing size.[29] These results also suggested that diagnostic accuracy of CNB increased with the increase of harvested specimens.[27,29]

To the best of our knowledge, this is the first study to evaluate the correlation between the number of core biopsies obtained and an accuracy of histological types, nuclear grades, hormone receptors, and HER2 status. Statistically significant differences were detected between patients who received four or more cores and those who had received three or less cores in the discrepancy of the following factors between CNB and subsequent surgical specimens: histological types, nuclear grade, and PgR. In addition, a similar tendency was also detected in ER and HER2 as above, and the cases that received four cores reached to 100% concordance in diagnosis between CNB and surgical specimens. Therefore, the optimal numbers of CNB may be considered four cores, which represent sufficient volume for histopathologic diagnosis. Core biopsy can provide reliable information on histological types, invasion, nuclear grade, hormone receptors, and HER2 status of patients.

Acknowledgments

We appreciate Yayoi Takahashi, MT, for her excellent technical assistance. This work was partly supported by grants from the Ministry of Health, Labour and Welfare of Japan for Research on Intractable Diseases, Risk Analysis Research on Food and Pharmaceuticals, and Development of Multidisciplinary Treatment Algorithm with Biomarkers and Modeling of the Decision-making Process with Artificial Intelligence for Primary Breast Cancer. This work was also partly supported by a Grant-in-Aid for Scientific Research (18390109) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Yasuda Medical Foundation.

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JJCO Japanese Journal of Clinical Oncology

Original Articles

Jpn J Clin Oncol 2010;40(10)905–912
doi:10.1093/jjco/hyq070
Advance Access Publication 21 May 2010

The Correlation Between Ultrasonographic Findings and Pathologic Features in Breast Disorders

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Received January 9, 2010; accepted April 7, 2010

Objective: Breast ultrasonography has gained widespread acceptance as a diagnostic tool for the evaluation of human breast disorders. It is important to evaluate the correlation of ultrasonography findings with the corresponding histopathological features.
Method: We retrospectively reviewed the 154 cases of breast disorders. We evaluated the correlation the ultrasonography findings and carcinoma cells extension with their corresponding histopathological findings. In addition, we also studied the information on estimation of histological types and cancer extension used by the other modalities such as computed tomography and magnetic resonance imaging.
Results: The concordance rate for margins between ultrasonography findings and histopathological features was 91.6% ($P < 0.001$) and that for boundary zone was 87.0% ($P < 0.001$). Histopathological correlation of internal and posterior echoes demonstrated that internal low echo masses were composed of fibroblastic cells with marked collagenization in the stroma, or the cases in which carcinoma cells proliferated in a monotonous, solid and/or expanding manners. Attenuation of posterior echo was detected in the cases associated with hyperplasia of collagenized fibroblastic stroma. An increased cellularity in the mass with prominent large tumor nests and little fibrous stroma demonstrated the accentuation or no alterations of the posterior echo. The concordance rate of borders was 84.4% ($P < 0.001$). The correlation between estimated histological type by ultrasonography diagnosis and actual histological types was 87.0%. An overall detection rate of carcinoma extension by ultrasonography was 86.4%. In addition, an overall detection rate of carcinoma extension by ultrasonography, magnetic resonance imaging and computed tomography was 93.8%.
Conclusion: These results demonstrated correlation between histopathological and ultrasonographic findings of the breast lesions is cardinal for quality control or improving the quality of ultrasonography.

Key words: breast ultrasound – histopathologic findings – carcinoma extension

INTRODUCTION

Breast cancer has become one of the leading causes of death among women. Early clinical detection of breast cancer through screening has led to the detection of the tumor at a relatively earlier clinical stage, which definitely reduced its mortality. The mammographic appearance of breast carcinoma has been well known to vary greatly (1). On the other

hand, breast ultrasonography (US) has gained widespread acceptance as a diagnostic tool for the evaluation of breast disorders (2). It is true that some breast diseases that are obscured by dense breast tissue at mammography can be detected with US. US has been in general proposed to serve better in the detection of breast cancer if the patient is young or the masses are small (3,4). Results of many previously published studies have demonstrated the diagnostic benefits in differentiating benign from malignant breast disease in the evaluation using US (5). It was well known that carcinomas are classically described as irregular solid masses with a heterogenous texture and reduced sound transmission in the US, resulting in what is called 'shadowing' behind the lesion (5,6). In addition, a vertical orientation of the lesion is described more often in breast carcinoma in US evaluation (5,6). It is also true that not all carcinomas fulfill these criteria and some do only partially (5). In general, an accurate correlation of US findings with their corresponding histopathologic features is considered most important in US evaluation in this setting.

Breast-conserving surgery is being widely applied in the treatment of early breast cancer. In order to perform conserving surgery, it is very important to detect carcinoma extension and determine the excision area as accurately as possible in the preoperative setting for the benefits of the patients (7,8). Complete removal of a breast tumor with tumor-negative surgical margins is considered most important for avoiding local recurrence in breast-conserving surgery. With high-resolution equipment available, US can detect smaller non-palpable cancers not necessarily detected on high-quality mammography. Excellent visualization of extended intraductal component has been reported using US in some institutions (9,10). However, few have demonstrated the limitation of the US to detect small lesions. Therefore, we attempted to evaluate carcinoma infiltration based on US findings, through revealing histopathologic features of the carcinoma cells infiltration which cannot be detected by US. In addition, in order to overcome these possible limitations, magnetic resonance imaging (MRI) and computed tomography (CT) are being increasingly utilized for the preoperative evaluation of carcinoma extension (11–13). Therefore, we also evaluated the information regarding the detection of cancer infiltration by US in conjunction with MRI and CT.

It is very important to evaluate the correlation of US findings with the corresponding histopathological features. The purpose of this study is therefore, to evaluate the correlation of the US findings including shape, boundary zone, internal and posterior echo, anterior and posterior borders, estimated histological types and carcinoma infiltration with their corresponding histopathological findings of the same lesions. In particular, for internal and posterior echoes, attenuation has been considered to be provided by a highly cellular fibroblastic proliferation (2,14). However, none has ever reported that internal and posterior echo were indeed based on the ratio of intratumoral carcinoma cells and fibroblastic stroma, and histological stromal characteristics of the same lesions. We therefore indicated that anterior and posterior echoes were indeed caused by the ratio of intratumoral carcinoma cells and fibroblastic stroma, and histological stromal characteristics. In addition, some histological types demonstrated low concordance rates between estimated or the histological types estimated by ultrasonographic findings and actual histological types. Therefore, we also discussed this particular discordance between estimated US findings and histologic types, in detail.

Table 1. Histological types of examined cases

Histological types (all)	154
Invasive ductal carcinoma (IDC)	132
Ductal carcinoma in situ (DCIS)	7
Invasive lobular carcinoma (ILC)	10
Mucinous carcinoma	5

PATIENTS AND METHODS

Patients

We retrospectively reviewed the US findings and the histopathologic features of 154 breast lesions for which surgery was performed in Tohoku University Hospital from 1 January 2006 to 31 December 2007 and in which the patients were initially detected by US. The cases treated with neo-adjuvant chemotherapy were excluded from this study of correlating preoperative US findings with histopathlogical analyses. We received informed consents from the patients and the protocol for this study was approved by the Ethics Committee at Tohoku University School of Medicine. The median age of the patients was 57 years (range, 27–85). Of the remaining consecutive 154 patients, 132 were diagnosed histopathologically as invasive ductal carcinomas (IDC), 7 with ductal carcinoma in situ (DCIS), 10 with invasive lobular carcinomas (ILC) and 5 with mucinous carcinomas (Table 1).

US and Histopathologic Analyses

The US were assessed by one of experienced eight breast surgeons of Tohoku University Hospital. They got the consensus meeting of US for a week to standardize the US exam. In addition, two surgical oncologists independently evaluated the US findings in a retrospective manner, without the knowledge of subsequent histopathological diagnosis. These two investigators were also blinded to the clinical outcome of the patients. The US examination was carried out using the following mechanical scanners: Aloka SSD 3500 (Aloka Co., Tokyo, Japan) with a 10-MHz transducer.

Surgical specimens had been fixed in 10% formaldehyde solution and cut into serial 5-mm thick slices. Histopathological slides in each tumor were reviewed by two pathologists independently without knowledge of the breast US findings. They used Olympus (Tokyo, Japan) BX50 and 20X objectives for the analysis.

Of two or more hardcopy transverse and sagittal plane images of breast lesions, only the largest lesion was analyzed in this study. In the patients with multiple breast lesions, only the largest lesion was evaluated. US findings were subsequently analyzed according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) sonographic classification (2) and the Japan Association of Breast and Thyroid Sonology (JABTS) breast sonographic classification (14). The presence of a mass, margin, boundary zone, internal echoes, posterior echoes and associated findings were each recorded. Histopathological evaluations were based on the Japanese Breast Cancer Society (2008) (15), World Health Organization (WHO) histological classification of tumors of the breast (1) and Rosen's Breast Pathology (16). (i) Margin was tentatively classified into circumscribed or not and also histopathologically classified into these two categories above. (ii) For boundary zone, we analyzed the presence or absence of halo in US. Ultrasonographic 'Halo' corresponded to the histopathologic features in which carcinoma cells invade into fat tissue admixed with adipocytes and elastic fiber (14). We termed the histopathologic feature 'histopathologic halo' and evaluated the existence of the 'histopathologic halo' (Fig. 1). (iii) Internal echo was tentatively classified into low and equal/heterogenous, and posterior echo was tentatively classified into accentuating, no change and attenuating (14). Histopathologic features corresponding to internal and posterior echoic findings were defined by the ratio of carcinoma cells to stroma and the following characteristics related to stromal architecture; collagenization or poor collagenization. We analyzed the intratumoral stroma in five representative fields per case ($\times 200$) (Fig. 2). (iv) We analyzed relevant findings about interruption of the anterior and posterior borders of the mammary gland. Interruption of the borders demonstrated extension in adipose tissue, whereas non-interruption demonstrated extension in gland (Fig. 3). (v) We examined the concordance between the estimated and actual histological types. We estimated histological types as followings; IDC, DCIS, ILC and mucinous carcinoma by US without knowledge of histopathological diagnoses.

US, CT and MRI were performed prior to breast-conserving surgery. A 16-row detector CT system (Somatom Sensation Cardiac; Siemens Medical Solution, Erlangen, Germany) was used with CT skin marker, consisting of a paper seal and seven 75-mm non-lead lines with an open window between each line, over the location of the target (13). The breast MRI was obtained using a 1.5 tesla MRI clinical scanner (Magnetom Vision, Siemens, Erlangen, Geramany) (17). The histopathologic diagnosis and the carcinoma extension in all slices were determined by the two pathologists. The surgical margin was defined as positive margin when there were malignant cells at the surgical margin and within 5 mm of the surgical margin. The accurate ratio between the cancer extension detected by the US and the histopathologic cancer extension was evaluated. We also studied the information on detecting cancer extension used by the other modalities such as CT and MRI. In addition, the histopathological characteristics of the cases which could not to be detected by the US were also evaluated. If there were discrepancies of carcinoma extension and estimated histological types among these modalities, we returned to examine the discrepant lesions by US again. When the US findings of the lesions represented desmoplastic change or stromal reaction, we accepted the diagnoses by MRI and CT. On the other hand, when the US findings represented normal variations, we accepted the US diagnoses.

Statistically analysis, such as the one-factor ANOVA and simple regression analysis, were performed using StatMate III for Windows ver. 3.18 (ATMS, Tokyo, Japan). The results were considered significant at $P < 0.05$.

RESULTS

Evaluation of the Margins of the Lesion

Twenty-six out of the 154 were circumscribed masses. Of the 26 circumscribed tumors detected by US, 18 cases

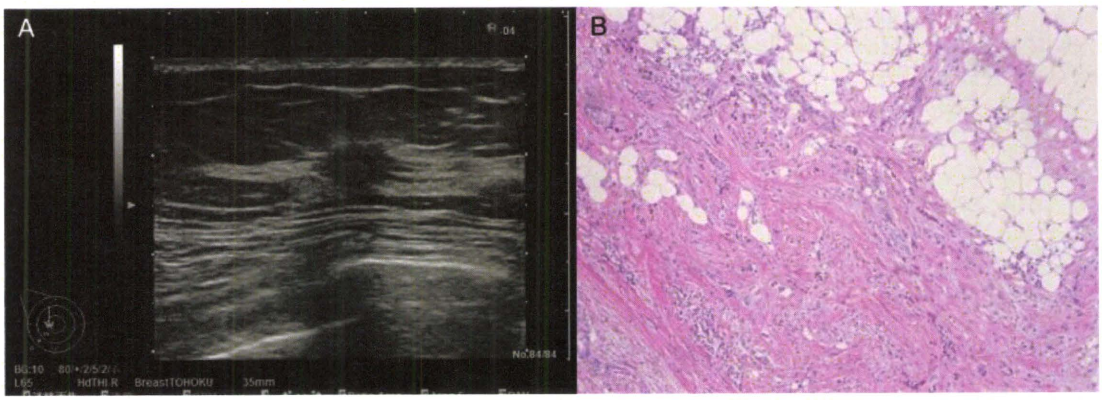

Figure 1. Representative illustrations of 'halo'. (A) 'Halo' of the US finding. (B) The histopathologic feature representing infiltration of carcinoma cells into the surrounding tissues, such as fat tissue and elastic fiber.

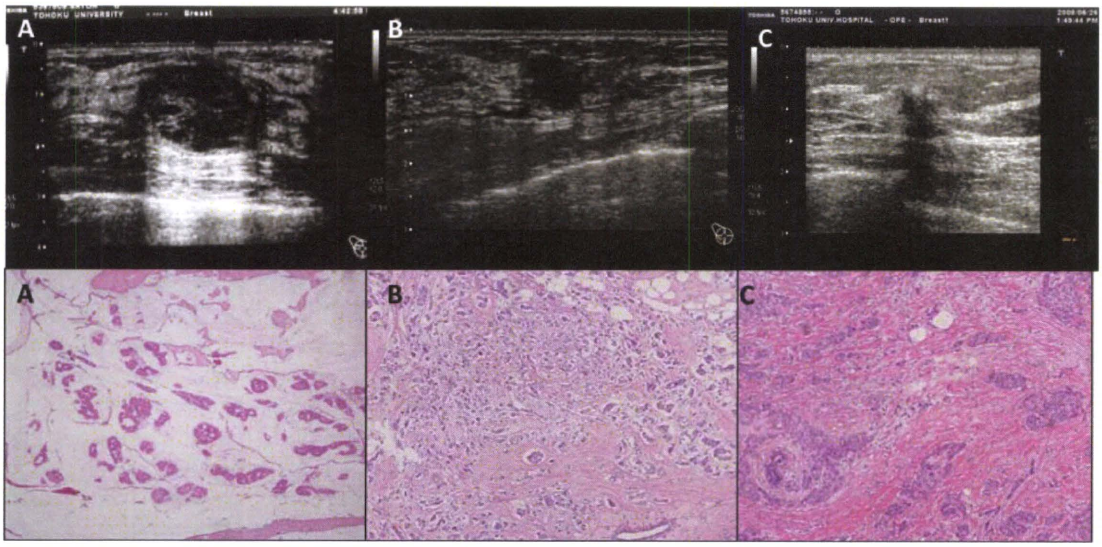

Figure 2. Representative illustrations of internal echoe and posterior echoe. (A) Shows internal echo is heterogenous and posterior echo is accentuating. The histologic type is mucinous carcinoma in which intratumoral structure is heterogenous and constructed by mucin. (B) Shows internal echo is low or hetrogenous and posterior echo is no change. The intratumoral histopathologic feature is heterogenous and poor collagenized stroma. Whereas (C) shows internal echo is low and posterior echo is attenuation. The intratumoral histopathologic feature is heterogenous but the stroma is marked collagenized.

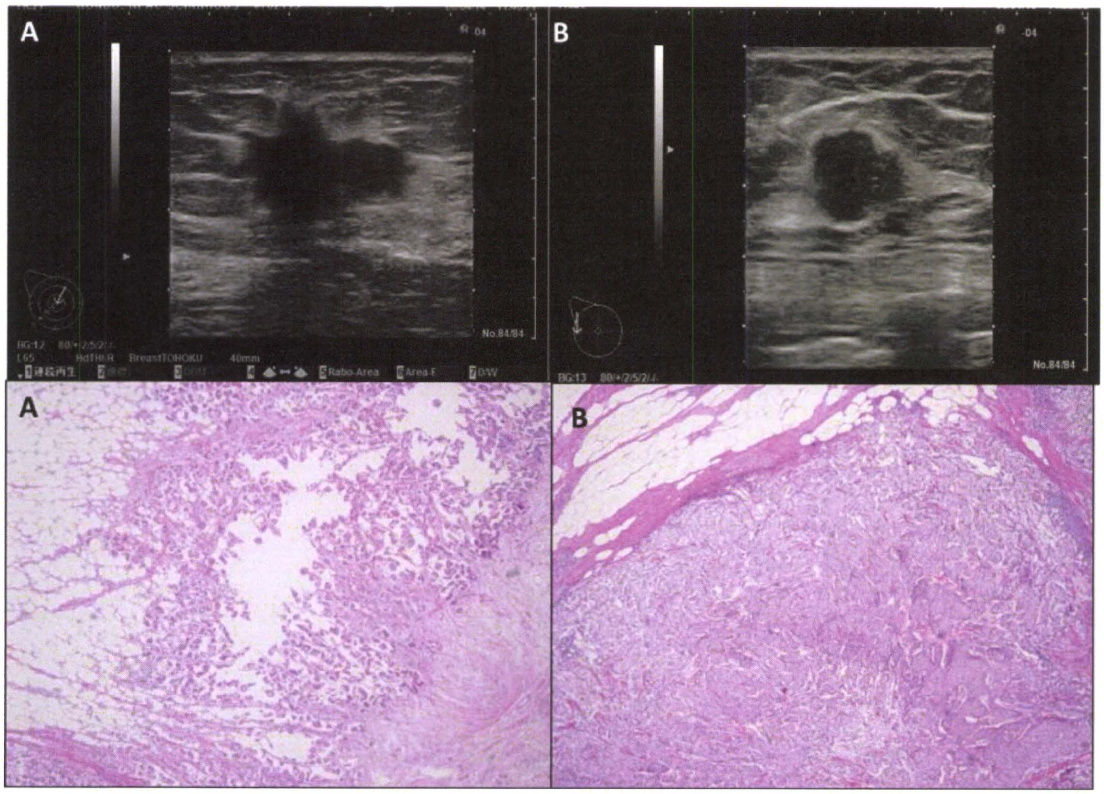

Figure 3. Representative illustrations of interruption and not interruption of the mammary borders. (A) Shows interruption of the anterior border. Histopathologically, carcinoma cells extend to fat. (B) Shows not interruption of the borders. Histopathologically, carcinoma cells extend in the mammary gland.

(69.2%) were also histopathologically circumscribed. Not circumscribed masses were 128 tumors in our present study. One hundred and sixteen out of these 128 tumors (90.6%) were also histopathologically 'not circumscribed'. The rate of concordance between US and histopathological findings was 87.0% ($P < 0.001$).