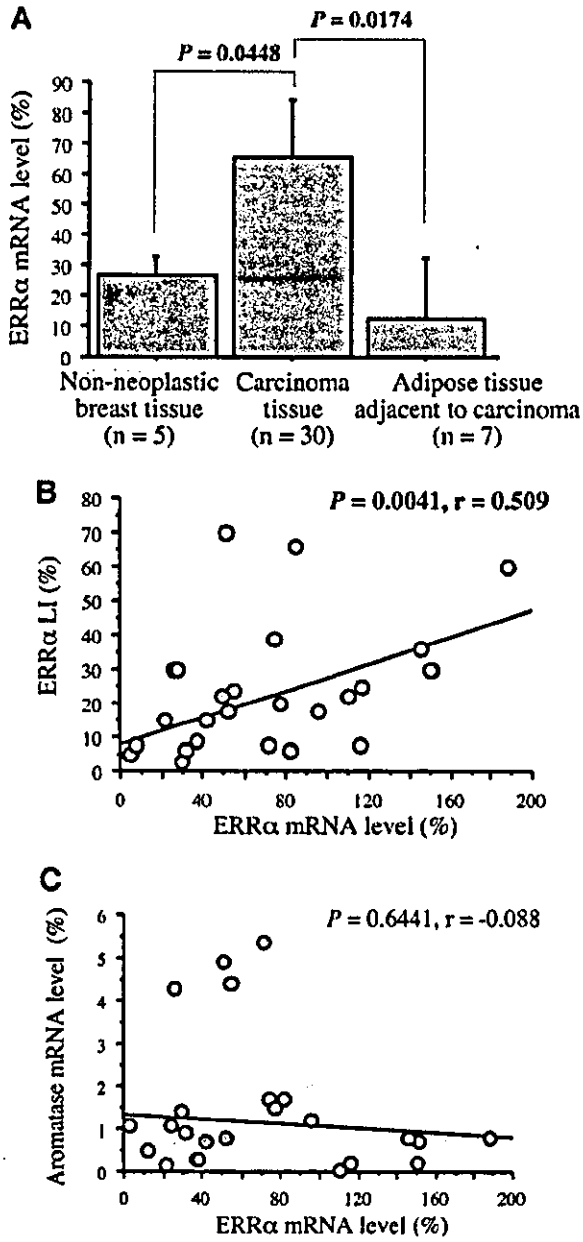

Fig. 3. Real-time reverse transcription-PCR for ERRα in the breast carcinoma. *A*, expression of ERRα mRNA was significantly higher in the breast carcinoma tissues (65.7 ± 9.0%, n = 30) than in non-neoplastic breast tissues [25.4 ± 6.0% (n = 5), P = 0.0448 *versus* carcinoma tissues] or adipose tissues adjacent to the carcinoma [12.6 ± 7.3% (n = 7), P = 0.0174 *versus* carcinoma tissues]. Data represent the mean ± 95% confidence interval. The mRNA level of ERRα in each specimen was evaluated as a ratio (%) of the positive control tissue (human heart tissue = 100%). *B*, association between the mRNA level and relative immunoreactivity (labeling index) of ERRα in 30 cases of breast carcinoma tissues. Significant positive association was detected (P = 0.0041, r = 0.509). *C*, association between ERRα and aromatase mRNA levels in 30 breast carcinoma tissues. No significant correlation was detected (P = 0.6441, r = −0.088). Aromatase mRNA expression in each case was evaluated as a ratio (%) of that in the human placental tissue. *ERR*, estrogen-related receptor α.

ERRα immunoreactivity was also associated with poor prognosis in the group of breast cancer patients who received tamoxifen therapy, which suggests that ERRα status is a possible predictive marker for tamoxifen therapy, although the number of cases examined was limited in this study. Previous *in vitro* studies demonstrated that both tamoxifen and 4-hydroxytamoxifen did not bind to ERRα or did not have any effects on the transcriptional activity of ERRα, whereas these are high-affinity ligands for ERRβ or ERRγ (41, 42). Therefore, ERRα may constitutively function independently of tamoxifen and result in tamoxifen resistance in ERRα-positive breast cancer patients.

Aromatase is a key enzyme in *in situ* estrogen biosynthesis in breast cancer tissue, and aromatase inhibitors are currently used in breast cancer patients as an endocrine therapy as well as antiestrogens. Aromatase is markedly activated by SF1 through an SF1-binding element within the promoter region (43). However, SF1 is not expressed in breast carcinoma tissues (11, 44). Previously, Yang *et al.* (11) reported the induction of aromatase expression by ERRα through a SF1-binding element in breast fibroblast, suggesting the possible importance of ERRα as a regulator of aromatase expression in breast cancer. However, in our study, we did not find ERRα immunoreactivity in the intra-tumoral stromal cells or adipocytes adjacent to the carcinoma, although these cells are well-known to express aromatase (45). Previous *in vitro* studies have shown the regulation of aromatase transcription in breast fibroblasts and/or adipocytes by various factors, including cytokines (46), prostaglandin E_2 (47), liver receptor homologue-1 (44) and CCAAT/enhancer-binding protein β (48).

In summary, ERRα immunoreactivity was detected in carcinoma cells in 55% of breast cancer tissues and was associated with its mRNA level. Association between ERα and ERE-containing estrogen-responsive genes was markedly altered according to ERRα status in the breast cancer tissues. ERRα immunoreactivity was associated with poor prognosis of the patients, and similar tendency was also detected in the group who received tamoxifen therapy. These findings suggest that ERRα possibly modulates the expression of ERE-containing estrogen responsive genes, and ERRα immunoreactivity is a potent prognostic factor, including a possible predictive marker for tamoxifen resistance, in human breast carcinoma.

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Case Reports

MRI Accurately Depicts Underlying DCIS in a Patient with Paget's Disease of the Breast Without Palpable Mass and Mammography Findings

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Breast-conserving therapy must be carefully indicated among patients with Paget's disease of the breast, because the disease is often associated with an underlying *in situ* or invasive carcinoma, even when there are no palpable mass or mammography findings. We report a 52-year-old woman who complained of skin color change of her right nipple for 11 months. No mass was palpable in her breasts, and mammography did not show any density or calcification. Nipple biopsy revealed Paget's disease of the breast with ductal carcinoma *in situ* (DCIS) in the breast epithelium just beneath the nipple. Magnetic resonance imaging (MRI) of the breast demonstrated diffuse segmental enhancement in two different quadrants. According to the pattern of enhancement, the lesions depicted by MRI were diagnosed as an extensively spreading type of DCIS. Based on informed consent, the patient received a total mastectomy. The histopathological examination demonstrated non-invasive ductal carcinoma with comedo-necrosis. The histological mapping with subserial sectioning demonstrated an extent of the lesions that corresponded accurately to the lesions defined by MRI. We conclude that MRI may play an important role in selecting candidates for breast-conserving therapy, out of those patients with mammary Paget's disease with no clinical evidence of an underlying breast carcinoma.

Key words: Paget's disease – breast carcinoma – MRI – ductal carcinoma in situ

INTRODUCTION

The treatment for patients with Paget's disease of the breast is controversial. The standard treatment has been mastectomy (1,2). However, some studies have proposed the use of breast-conserving therapy for patients with Paget's disease in whom an underlying breast cancer cannot be located (3,4).

Nevertheless, other investigators reported that wide local excision of the nipple–areola complex and underlying breast tissue (cone excision) would have been insufficient surgery in 40% of their cases with no palpable mass and a normal mammogram, because of the multicentricity of the disease (5). Therefore, candidates for breast-conserving therapy must be selected carefully on an individual basis among those patients who have Paget's disease of the breast (6–8).

Here we report a case of a mammary Paget's disease patient who did not present either palpable mass or mammography findings. Magnetic resonance imaging (MRI) of the breast was very useful for making a decision on the appropriate surgical procedure.

CASE REPORT

A 52-year-old woman visited our hospital in January 2004 for an 11 month history of skin color change of her right nipple. She had also worried about the exudates from the nipple for 3 months. Physical examination showed the flattening and scaling of the nipple (Fig. 1). No mass was palpable in her breasts, and mammography did not reveal any density or calcification. There was also no abnormal finding on ultrasonography. Exfoliative cytology of the nipple demonstrated Paget's cells. To determine the surgical procedure of choice, MRI of the right breast was investigated. There were diffuse segmental enhancements existing in the upper and lateral quadrants (Fig. 2). According to the pattern of enhancement,

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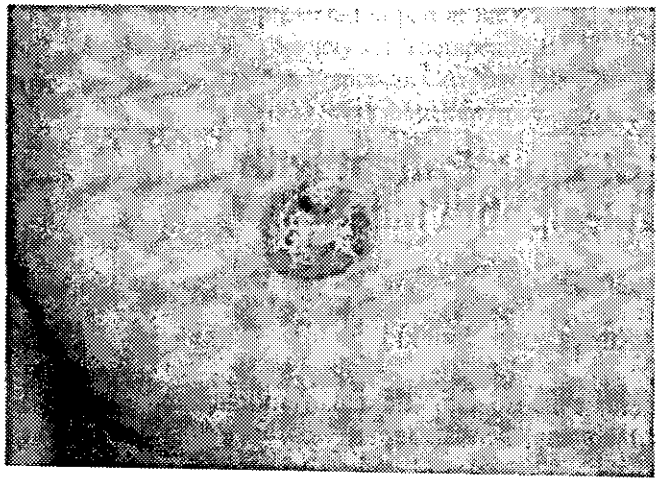

Figure 1. Flattening, scaling and color change of the right nipple were noted.

the lesions depicted by MRI were diagnosed as an extensively spreading type of ductal carcinoma *in situ* (DCIS). In an attempt to excise all the suspicious lesions, we recommended mastectomy to the patient, to which she gave her consent.

Prior to mastectomy, nipple biopsy was performed to confirm the histopathlolgical diagnosis of Paget's disease (Fig. 3A). Additional DCIS was also demonstrated in the breast epithelium just beneath the nipple (Fig. 3B).

On March 1, 2004, modified radical mastectomy was performed. The specimen was subserially sectioned in 7 mm thick slices, and every block was examined histopathologically. Non-invasive ductal carcinoma with comedo-necrosis was present (Fig. 4). Cytonuclear grade was grade 2 and estrogen/progesterone receptor status was negative. HER-2 was strongly (3+) immunoreactive. These cytological and immunohistochemical results were similar to those of Paget's cells in the nipple biopsy specimen. Lymph node metastasis was not

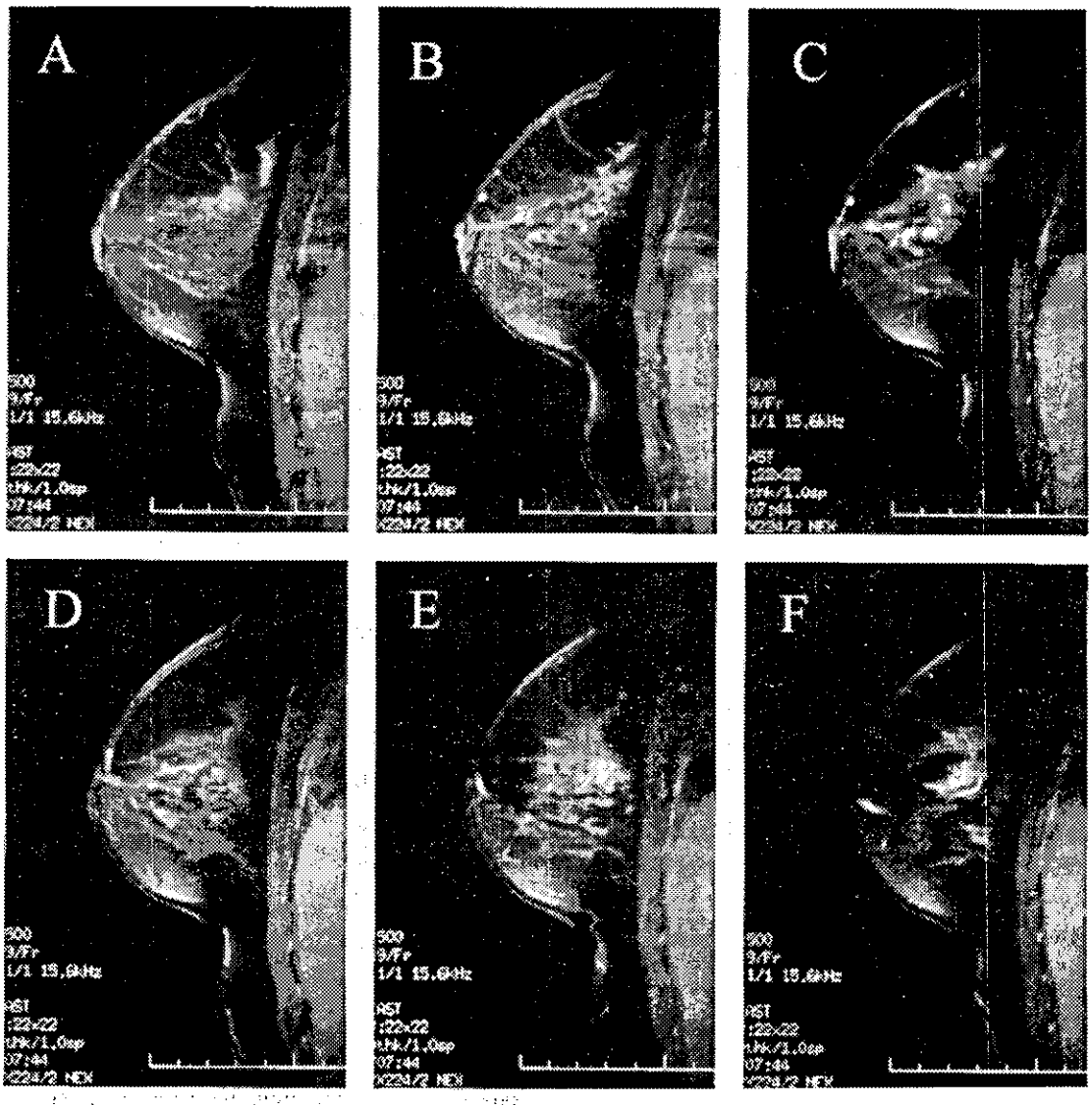

Figure 2. Fat-saturated, contrast-enhanced MRI of the right breast in the sagittal plane. From (A) to (F), a more lateral plane is shown at 6 mm intervals. (A–C) A diffuse segmental enhancement was apparent in the upper quadrant. (D–F) Another segmental enhanced lesion was shown in the lateral quadrant. The scale is graduated in centimeters.

Figure 3. (A) A photomicrograph of a cross-section of the nipple biopsy specimen shows the Paget's disease. Large, round or ovoid intraepidermal Paget's cells with abundant clear cytoplasm and enlarged pleomorphic nuclei are present (H&E, objective: ×10). (B) A photomicrograph of a cross-section of the nipple biopsy specimen shows additional DCIS in the breast epithelium just beneath the nipple (H&E, objective: ×10).

Figure 4. A photomicrograph of a cross-section of the mastectomy specimen shows non-invasive ductal carcinoma with comedo-necrosis (H&E, objective: ×4).

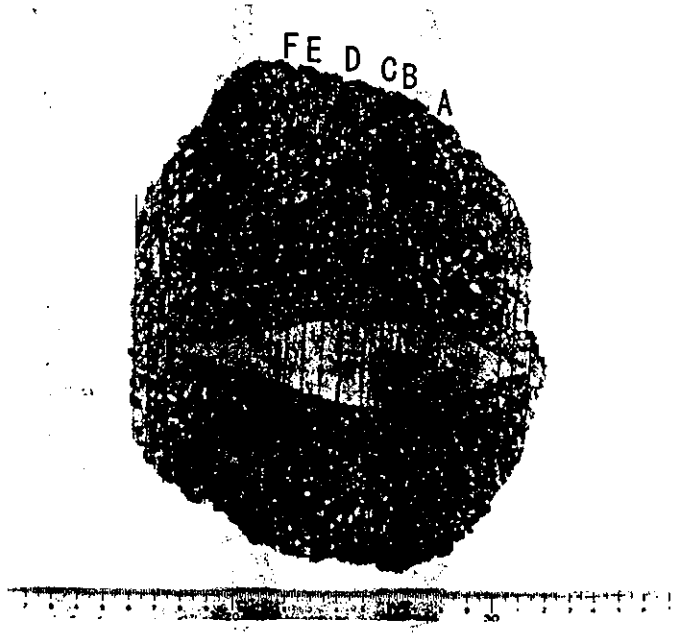

Figure 5. A histopathological cancer map of the mastectomy specimen, with the red marks denoting DCIS, reveals the extent of the lesions that are spreading in the upper and lateral quadrants. A–F indicate the location of the sliced specimen shown in Fig. 6. The scale is graduated in centimeters.

detected. According to the cancer map, DCIS were demonstrated extensively in the upper and lateral quadrants (Figs 5 and 6), accurately corresponding to the lesions shown by MRI (Fig. 2).

DISCUSSION

Paget's disease of the breast is a rare malignancy of the nipple–areola complex, comprising 0.5–5% of all breast cancer (1,7,9). It is manifested by progressive eczematoid changes of the areola with persistent soreness or itching (1,2,7). There have been debates about the histogenesis of this disease. According to the fact that this disease has been reported to be associated with an underlying breast carcinoma in 87–100% of cases (1–3,5–10), the epidermotropic theory, which postulates that Paget's cells are ductal cells that have migrated from an underlying breast carcinoma to the epidermis of the nipple, seems acceptable. The present case, where there existed underlying DCIS spreading extensively, is also compatible with the epidermotropic theory.

The treatment for patients with Paget's disease of the breast is controversial. Those patients with a palpable mass have a much greater incidence of invasive cancer, multifocal diseases, lymph nodal involvement and poor prognosis (1,2,6–8,10). Therefore, modified radical mastectomy is often the most appropriate treatment for patients with Paget's disease with a palpable lesion. On the other hand, for patients with Paget's disease who present no palpable mass, some investigators have proposed the use of breast-conserving therapy. Bijker et al. demonstrated that cone excision and radiotherapy is a feasible alternative for patients with Paget's disease and a limited extent of underlying DCIS (3). They reported a 5-year local

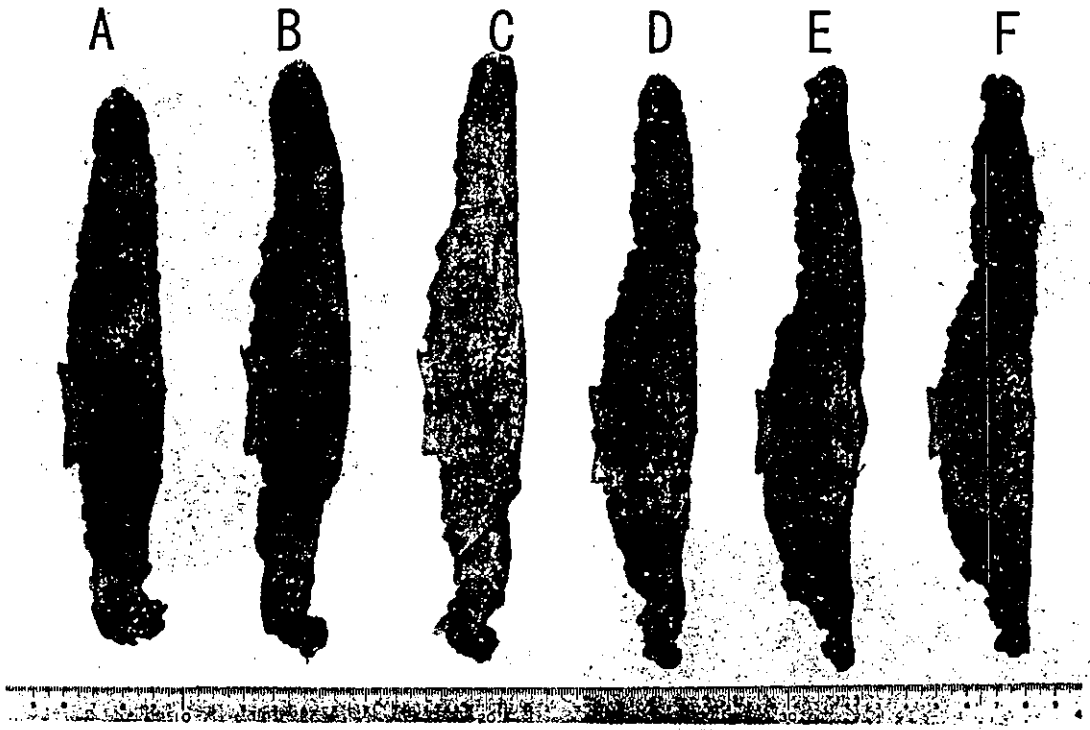

Figure 6. A more precise cancer map drawn on the cut surface of the mastectomy specimen. From (A) to (F), a more lateral plane is shown, and the location of the sliced specimen is indicated in Fig. 5. Note that the extent and distribution of DCIS, denoted by the red marks, correspond accurately to the enhanced lesions depicted by MRI in Fig. 2.

recurrence rate of 5.2%. Marshall et al. also recommended local excision and definitive breast irradiation as an alternative to mastectomy for patients with Paget's disease presenting no palpable mass or mammographic density (4). In their report, 5- and 10-year local control rates are 91 and 83%, respectively.

On the contrary, Kothari et al. warned against using breast-conserving therapy (5). They retrospectively reviewed the cases of 70 women with a clinical diagnosis of Paget's disease. Despite the fact that only one-third of women presented with a palpable mass, the malignancy was frequently extensive, being confined to the retroareolar region in only 25% of cases. They also demonstrated that the true extent of the disease was underestimated by mammography in 43% of cases. Of the 10 patients with no palpable mass and a normal mammogram, 40% had multicentric or multifocal carcinoma which would have been incompletely excised by cone excision of the nipple. Fu et al. described that of eight patients with no palpable mass who had been treated by quadrantectomy, two (25%) patients had recurrence (8). They concluded that even if the patient has no palpable mass, conservative surgery should be selected cautiously because of a higher recurrence rate and multifocal lesions.

In an era when breast-conserving surgery is sometimes recommended even for advanced infiltrating breast tumors, it seems quite reasonable to propose breast-conserving therapy for patients with Paget's disease with no definitive underlying breast cancer. However, as is already widely known, Paget's disease of the breast has a very high incidence of being accompanied by an underlying invasive or *in situ* carcinoma, even when there is no palpable mass (1–6,8–10). Mammography often fails to demonstrate the true extent of the disease (3–6,9). A more accurate and reliable imaging modality is necessary to select candidates for breast-conserving therapy more safely from among the patients who have Paget's disease of the breast.

Clinical utilization of MRI for breast cancer diagnosis has been under investigation since the late 1970s. With advances in surface coil technology and new imaging protocols using intravenously administered gadopentetate dimeglumine, MRI of the breast can now detect invasive cancer with 98–100% sensitivity (11,12). Amano et al. demonstrated that MRI can also detect the extensively spreading type of DCIS, that is often occult clinically and mammographically, as a pattern of diffuse segmental enhancement (13). In their study, the sensitivity of MRI to detect the extensively spreading type of DCIS was calculated to be up to 100%, and the specificity was estimated as high as 95%. The role of MRI in determining the extent of breast cancer is now well established (14). In the present case, no mass was palpable in her breasts, neither was there any abnormal findings on mammography or ultrasonography. There seemed a chance for her right breast to be treated conservatively, and for that reason we investigated it by MRI. There were diffuse segmental enhancements in the upper and lateral quadrants, strongly indicating the extensively spreading type of DCIS. Post-operative histopathological examination demonstrated non-invasive ductal carcinoma

with comedo-necrosis in the upper and lateral quadrants. The histological mapping with subserial sectioning demonstrated an extent of the lesions that corresponded accurately to the lesions defined by MRI. We conclude that MRI may play an important role in selecting candidates for breast conserving therapy out of those patients with mammary Paget's disease with no clinical evidence of an underlying breast carcinoma.

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Review Article

Ductal Carcinoma *in situ* and Related Lesions of the Breast: Recent Advances in Pathology Practice

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The incidence of ductal carcinoma in situ (DCIS) of the breast has increased significantly in Japanese women. It comprises 14.1% (172/1216) of all primary breast cancers at our institute, and nowadays this histological type is familiar to the surgeons and pathologists of any institute.

Several subclassifications have been published recently. Most based on nuclear atypia and the presence of comedonecrosis, and sometimes on the structures of the involved glands. These classifications are correlated with the biological behavior, tumor extent and the risk for local recurrences. The diagnostic accuracy of minimally invasive procedures (aspiration biopsy cytology/core needle biopsy) may differ between subclasses.

Atypical ductal hyperplasia (ADH) and microinvasive ductal carcinomas are lesions which resemble but deviate from the DCIS spectrum. The incidence of ADH seems to be lower than in Western countries. Patients with ADH may have a risk for subsequent breast cancer, because ADH is frequently associated with contralateral breast carcinomas. Microinvasion should be treated with caution, but we could not find any metastatic foci in microinvasive ductal carcinomas (T1mic). Tentatively, ADH may be treated similarly to non-comedo (low-grade) DCIS cases, according to our limited clinical experience.

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Key words: Breast, Ductal carcinoma *in situ*, Atypical ductal hyperplasia, Intraepithelial neoplasia, Microinvasive carcinoma

Recently, the incidence of ductal carcinoma *in situ* (DCIS) of the breast has increased, probably because of the early detection of cancer, especially by screening mammography. Nowadays, it is well known that DCIS is a heterogeneous group of diseases, both morphologically and biologically. Thus, further subclassification is recommended after this tumor is diognosed. Moreover, recent advances in less invasive diagnostic procedures has increased the chances for diagnostic pathologists to diagnose problematic intraductal lesions. These include questionable lesions suspicious for carcinoma, based on either fine needle aspiration cytology (FNAC) or core needle biopsy (CNB) results, and lesions that are definitely carcinoma of ductal origin, the invasiveness of which however cannot be determined by CNB. Additionally, the concept of intraductal proliferative lesions has been advanced to stratify lesions that pose different risks for the development of subsequent invasive carcinoma[1]. We will review recent advances in the field and the current situation in Japanese women.

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Incidence of DCIS

DCIS was not frequent several decades ago. Since the 1980's its incidence has progressively increased, especially in western countries. In the USA, CIS (most of them were DCIS) incidence rates increased between 1973 and 1997 (under 50 years old, white 146%, black 283%; and over 50 years old, white 308%, black 349%)[2]. In 1997 CIS accounted for 16.4% of all breast carcinomas in white women, and 18.6% in black women[3]. In Los Angeles County, the average annual age-matched

incidence of CIS increased more than 5-fold between 1972-1981 and 1997-1998 (3.8 to 17.7/100.000 women), and the ratio of increase was higher than that of invasive carcinomas (86.1 to 111.5). The ratio of CIS among all breast carcinomas has increased from 4.2% (1972-1981) to 15.0% (1997-1998)[4]. National surveillance in Japan from 1980 to 1990 revealed that the ratio of CIS was between 2 to 4%, and had gradually increased[4]. The ratio of CIS among non-palpable breast carcinomas was more than 50% in most of series in Japan[4]. Considering the development of mammographic detection of breast carcinoma during the past two decades, it is not surprising that the ratio of DCIS has increased substantially.

It is necessary to note the methods of pathologic examination used to diagnose DCIS, because more precise examination may detect a minute focus of invasive carcinoma. Invasiveness is associated with the ability to metastasize. It is desirable to examine the lesions as closely as possible. However, this precision will be limited in routine practice. If the diagnoses of DCIS is made, the manner of the pathological examination is very important. We usually examined resected specimens from lumpectomy or larger operations by serial sectioning every 3-5 mm of the whole specimen (for cases of breast conserving surgery) and parenchyma (for cases of total mastectomy). By these methods, we detected 172 DCIS cases (14.1%) among 1,216 breast carcinomas between December 1998 and March 2002. The significance of DCIS diagnosed by CNB will be discussed later.

Subclassification of DCIS

DCIS represents a spectrum of disease, and the main purpose of subclassification is to stratify the risk of subsequent invasive carcinoma and/or local recurrence[5]. A rare exception is the classification by growth pattern (microfocal, diffuse, and tumor forming) according to mammographic or gross findings[6].

Previously, the microarchitecture was thought to be the most reliable feature[7,8]. Any architectural pattern may present with any nuclear grade, with or without necrosis. The simplest ways of subclassification is separating comedo from non-comedo lesions. Comedo type DCIS cases may have higher nuclear grade (by definition in many articles), larger tumor size, aggressive biological marker expression, and a higher risk of the (micro) invasion[9-13]. Close to 90% of palpable, pre-mammographic DCISs were reported as high grade comedo type lesions. In contrast, nearly 60% of mammographically detected lesions are the non-comedo subtype[14]. The incidence of the latter group is increasing. Architectural patterns other than comedo included cribriform, papillary, micropapillary (low papillary), solid, and mixed subtypes[5,10].

One of the problems using the term "comedo" DCIS is that the definition is not uniform. Variable criteria have been employed according to the proportion of comedonecrosis, architecture, nuclear grade, and a combination of these characteristics for the same category[16]. Additionally, it is not easy for pathologists to fit each DCIS into an architectural classification. In such cases, the term mixed subtype may be used, but many DCIS cases may therefore be classified as mixed. Thus, the employment of architectural subdivision may not always be reliable. Various pathologic subclassifications, using other than architectural features, have since been proposed.

Both nuclear grade and necrosis are thought to be more reliable predictive factors than architecture by some authors[9,10,13], and some of the new subclassifications employ mainly nuclear atypia (nuclear grade), or a combination of nuclear atypia and necrosis[17-20]. Some studies enhanced interobserver reproducibility by using subclassifications devoid of architecture[21-25]. However, the architecture may be correlated with nuclear atypia, and some classifications still recommend describing the architecture along with stypia. Table 1 shows the relationship between architecture, nuclear atypia, and other findings of DCISs published previously[9], and the current van Nuys classification[16]. The predominant architectural patterns may correlate relatively well with the new grading system, although it is devoid of architecture. Additionally, there is some evidence that the micropapillary architectural type, when present in its pure form, is more commonly associated with more extensive, multifocal and multicentric disease[7,15].

One of the classifications employing an architectural description is the proposed classification of DCIS by the study group of the Japanese Breast Cancer Society (Table 2)[5]. The new WHO classification described three tier grading (low/intermediate/high grade), mainly according to nuclear features. The presence and absence of necrosis,

Table 1. Predominant Architecture of DCIS and their Comparison with the van Nuys Classification

Predominant architecture	COM	C + N	M + N	S + N	CRB	MCP	SOL	OTH	Total (or average)
No. of cases	7	3	7	6	22	19	9	12	85
NG 3	7								7
2		3	7	6	8	6	8	9	47
1					14	13	1	3	31
van Nuys Group	3	2	2	2	1	1	1	any	
mitotic counts; marked	4/7	2/3	1/7	2/6	0/22	2/19	1/9	2/12	17/85
mean No. of duct profiles involved	846	71	156	34	53	88	133	108	140
Maximum diameter (cm)	1.6	0.8	1.1	0.6	0.6	1.1	1.1	0.9	0.9

Van Nuys Group 3: high grade nuclei, Group 2: non-high grade nuclei with necrosis, Group 1: non-high grade nuclei without necrosis, COM: comedo, defined by high-grade nuclei, with solid nests and central necrosis, C + N: cribriform with necrosis, M + N: micropapillary with necrosis, S + N: solid with necrosis, CRB: cribriform, MCP: micropapillary, SOL: solid, OTH: others or mixed types

Table 2. Intraductal Proliferative Lesions: Different Terminology used in the Different Classification and their Relationships

Traditional terminology	Proposal by the study group, Japanese Breast Cancer Society, 2000	WHO classification 2003
Usual ductal hyperplasia (UDH)	Proliferative ductal lesions without atypia (mild/moderate-florid)	Usual ductal hyperplasia (UDH)
Flat epithelial atypia	Proliferative ductal lesions with atypia	Ductal intraepithelial neoplasia, grade 1A (DIN 1A)
Atypical ductal hyperplasia (ADH)	Proliferative ductal lesions with atypia (including ADH)	Ductal intraepithelial neoplasia, grade 1B (DIN 1B)
Ductal carcinoma in situ, low grade (Grade 1)	DCIS, HG 1 (low grade)	Ductal intraepithelial neoplasia, grade 1C (DIN 1 C)
Ductal carcinoma in situ, intermediate grade (Grade 2)	DCIS, HG 2 (intermediate grade)	Ductal intraepithelial neoplasia, grade 2 (DIN 2)
Ductal carcinoma in situ, high grade (Grade 3)	DCIS, HG3 (high grade)	Ductal intraepithelial neoplasia, grade 3 (DIN 3)

HG; histological grade

architectural feature, size of the lesions, and other characteristic features are also explained together[1]. If the different grade lesions are admixed within the same tumor, the description of their proportion is recommended. In any classification, the three-tier subdivision is always used, and the interrelationships between classifications are obvious. We employ the van Nuys classification currently, but we believe that it could be translated directly into the WHO classification in most cases.

Table 3 shows our recent experience of 82 cases of DCISs. The operative procedures consisted of 21 total mastectomies, 12 quadrantectomies, 37 wide excisions, 4 duct-lobular segmentectomies and 8 local excisions. All the cases were diagnosed by pathological examination of the whole tumor using 3-5 mm slices. By definition, all of the high-nuclear grade cases were classified into Group 3. The Group 1 cases were either of low or intermediate nuclear grade, but all of the Group 2 cases showed intermediate nuclear grade. Characteristically, the Group 3 cases showed a lower incidence of positive hormone receptor status ($p < 0.001$), and a higher incidence of HER-2 positivity ($p < 0.001$) compared with non-Group 3 cases. The results imply that nuclear grade will correlate well with hormone receptor/HER-2 neu status in DCIS cases. Additionally, although some authors reported a few cases (incidence 1-2%) of node-positive DCIS[15], we did not encounter any in our

Table 3. van Nuys Classification of DCIS and the Relationships between other Clinicopathological Features (Tohoku University Hospital 2002.6-2003.11)

Van Nuys Group	1	2	3	Total
Definition	non-high grade nuclei without necrosis	non-high grade nuclei with necrosis	high grade nuclei with/without necrosis	
No. of cases	39	30	13	82
NG 1/2/3	20/19/0	0/30/0	0/0/13	20/49/13
Age (average)	33-78 (54.4)	42-79 (54.1)	40-75 (59.2)	33-79 (55.0)
ER positive cases	33/34 (97.1%)	23/27 (85.2%)	2/10 (20.0%)*	58/71
PR positive cases	31/34 (91.2%)	22/27 (81.5%)	4/10 (40.0%)**	57/71
HER2 positive cases	2/32 (6.3%)	5/26 (19.2%)	7/10 (70.0%)***	15/68
Cases with lymph node positive	0/14	0/17	0/6	0/37

NG: Nuclear grade, ER: estrogen receptor, PR: progesterone receptor
*, **: significantly less frequent than non-Group 3 cases ($p < 0.001$)
***: significantly more frequent than non-Group 3 cases ($p < 0.001$)

series.

The unusual, rare subtypes include apocrine, mucinous, signet-ring cell, solid & papillary, spindled, neuroendocrine, Pagetoid, squamous, and clear. Most of these are classified according to their characteristic cell differentiation, rather than their architecture. Flat type DCIS, previously called clinging DCIS, may be a unique variant, which may resemble blunt duct adenosis on scanning magnification[26]. These lesions are malignant based on their genetic alteration[27], but are practically very difficult to diagnose accurately, especially low-grade lesions. More experience as well as further investigations will be necessary.

Differential Diagnoses of DCIS and Benign/Atypical Lesions

There are several lesions confused with DCIS in routine practice. They range from benign or borderline (atypically proliferating) intraductal lesions to minimally (micro-) invasive ductal carcinoma. Lobular neoplasia (atypical lobular hyperplasia and lobular carcinoma *in situ*) is another consideration.

Minimal Requirement to Diagnose DCIS

Low grade DCIS should be differentiated from benign and borderline (atypically proliferating) intraductal lesions. There have been several studies and proposals, including two famous studies by Page and colleagues, and Tavassoli[28, 29]. The new WHO classification employed both morphological and size criteria, probably according to these articles[1]. Morphologically, a monotonous cell population, high nuclear/cytoplasmic ratio, round nuclei, and hyperchromasia are necessary, combined with some architectural patterns. The evaluation of size has not been universally accepted. The entire involvement of 2 spaces, or cross section(s) exceeding 2 mm, are used for the minimal size.

The pathologist should pay great attention in routine practice to differentiate low-grade DCIS from intraductal hyperplasia or atypical ductal hyperplasia (ADH). A consensus conference on the classification of DCIS at Philadelphia in 1997[15] did not mention the precise distinction between DCIS and ADH, because they said it is difficult. Interobserver variability is sometimes problematic when intraductal lesions are diagnosed[30-32].

Intraductal Proliferative Lesions

Previously, proliferative disease of the breast was a form of epithelial hyperplasia usually seen with fibrocystic changes. Recently, the significance of these lesions has been enhanced, because they are related to carcinomas (whether directly or indirectly has not been proved, however), and early detection of low-grade carcinoma by mammography has also raised the incidence of precancerous proliferative lesions as well.

Currently, a new concept has emerged that describes intraductal proliferative lesions as a continuous disease entity, ranging from benign through atypical (ADH) to malignant disease

Table 4. Expression of Various Immunohistochemical Markers for Various Lesions (Including Intraductal) of the Breast

	UDH	ADH	DCIS		IDC	
			low grade	high grade	low grade	high grade
Average age	44.0	42.8	51.3	56.8	52.7	50.4
ER	5.7	6.7	6.4	5.0	5.8	3.3
PR	4.3	6.2	4.6	1.8	4.5	2.8
Ki-67 LI	3.7	4.5	9.5	9.4	21.3	35.9
p53	0/22	0/26	7/40			
c-erbB-2	0/22	0/26	8/40			

ER: estrogen receptor, PR: progesterone receptor, LI: labeling index, UDH: usual ductal hyperplasia, ADH: atypical ductal hyperplasia, DCIS: ductal carcinoma *in situ*, IDC: invasive ductal carcinoma (ER and PR were scored according to Allred DC et al. Mod Pathol 11: 155-168, 1998)

(DCIS)[29]. Even the concept of intraepithelial neoplasia (mammary intraepithelial neoplasia, MIN) has been adopted by some investigators[30]. The common loss of heterozygosity that occurrs with synchronous atypical ductal hyperplasia (ADH), DCIS and invasive ductal carcinoma (IDC) may suggest a stepwise progression from ADH to IDC[33]. However, smaller lesions are often removed by excision, and their real natural history is unknown. In practice, they are generally accepted to confer an increased risk for the subsequent development of invasive carcinoma, the magnitude of which varies according to the degree of proliferation and/or atypia[1]. In Japan, the study group of the Japanese Breast Cancer Society examined the interval to subsequent invasive carcinoma in the same quadrant of the breast after biopsy, and this was shorter in the cases showing a higher degree of intraductal proliferative lesions[5]. Table 2 shows the classification proposed by the the study group and its relationship between the new WHO classification[1, 5]. Table 4 shows the expression of some biomarkers analyzed immunohistochemically[33, 34].

Atypically proliferative lesions (atypical ductal hyperplaia-ADH/proliferative disease with atypia) are ductal proliferative lesions, which should be differentiated from DCIS histologically by the presence of structural and/or cytological atypia along with proliferative disease without atypia. This category may include the lesions with increased relative risk for subsequent invasive carcinomas, but their biological behavior and clinicopathological significance is uncertain, at least currently. Thus the diagnosis of "atypia" should be made with caution, and not used so frequently. If one uses this word on the pathological report, the reasons for the term "atypia" should be mentioned. For example, a description of the extent of the lesions, degree of epithelial proliferation, structural atypia, nuclear atypia or number of mitoses is recommended[5].

Atypical Ductal Hyperplasia (ADH)

ADH probably comprises the majority of "atypical" lesions but is also relatively rare. ADH may be diagnosed when one suspects but hesitates to diagnose DCIS, because of incompleteness of monotony (either structural or cytological) or limited extent. In any case, sufficient discussion with surgeons, and close follow-up is necessary.

At least in Japan, the diagnosis of ADH has not been widely accepted. We use this terminology in routine practice, according to the criteria of Page and colleagues[28]. They said that almost 3.5% of the biopsy specimens are diagnosed as ADH, however, we think that the incidence is much lower. This may be due to differences between Japanese and western populations or interobserver variability. We had a chance to review a biopsy series in which fibrocystic change was initially diagnosed, and found that the incidence of ADH was 1.2% by re-examination[35]. Table 5 shows the clinicopathological features of ADH cases in our laboratory. Only 21 cases were diagnosed as solitary ADH out of almost 1,000 primary breast cancer cases (cases with synchronous, ipsilateral carcinomas were eliminated, and consultation cases were not included). The patients were relatively young, as shown in Table 5. Interestingly, at least 5 cases

Table 5. Atypical Ductal Hyperplasia (ADH): Experience at The Pathology Department of Tohoku University Hospital from December 1998 to June 2002

- 21 case (cases with synclonous, ipsilateral carcinomas were eliminated)
- Background: 995 primary breast cancers, including 206 DCISs during the same period
- Age & gender: 28-56 (average 46.2) years old, all female
- Contralateral breast cancers: At least 5 cases (2 synclonous, 3 subsequent, follow-up period up to 5 years)
- Associated lesions: 3 were intermingled with papilloma, 1 with mucocele-like lesion, 1 within fibroadenoma
- Fine needle aspiration cytology: negative 5, indeterminate 6, suspicious for malignancy 3
- Diagnostic procedure: Local excision 15, Duct lobular segmentectomy 5, Core needle biopsy 1

showed contralateral breast cancer. This implies that ADH may be a relative risk for developing invasive breast carcinoma even in a population with a low incidence of ADH.

Microinvasive Ductal Carcinoma

The upper end of the DCIS spectrum is the borderline between DCIS and carcinoma with minimal stromal invasion. If invasion exists, there is a chance for metastasis. Variable definitions for "microinvasion" have been proposed previously. The cases with an invasive focus less than 1% of the total[1], or an invasive focus less than 1 mm (T1mic)[37] are relatively widely accepted to represent microvasion. They will show an apparent foci of infiltration into "interlobular" stroma. We have encountered 28 T1mic cases among 1,216 primary breast cancers (2.3%), and about 1/6 of DCIS cases (172 cases during the same period)[38]. Most were composed of small cell nests, or of single cells, but tongue-like projections with reactive stroma may be seen. There may be multiple foci (1-7 foci, average 3, in our series). These cases may show higher nuclear grade, tend to be associated with comedonecrosis, and more severe stromal reactions (lamellar fibrosis and/or chronic inflammatory cells) around the intraductal carcinomas.

Microinvasive carcinomas express a relatively low risk for lymph node metastases, and the prognosis is considered to be extremely good[39, 40]. None in our series expressed axillary lymph node metastases on serial sectioning of the whole carcinoma[38]. However, follow-up data using universally accepted procedures and/or criteria will be necessary to reach the final conclusions.

Diagnosis of DCIS and ADH by Minimally Invasive Procedures

Core needle biopsy (CNB) under stereo- or ultrasound guided procedures has been widely accepted. Thus, there has been an increased chance to diagnose earlier carcinomas (including low-grade DCIS) and borderline lesions. One of the problems of using this method is the specimen does not always include minute foci of invasion. If DCIS was diagnosed by CNB, there is still a chance for invasive carcinoma in the residual parenchyma. About 30% of DCIS diagnosed by CNB were truly invasive carcinoma in one study using a 14-gauge core[41], but the incidence fell to 10% with an 11-gauge vacuum-assisted procedure[42]. Similarly, if ADH is seen by core needle biopsy (CNB), 12-33% of the cases showed DCIS on excisional biopsy[43]. Some of the cases may be DCIS with invasion (IDC) but this situation is usually related to the number of foci (4 or more) of ADH on CNB[44].

Ultrasound-guided fine-needle aspiration biopsy cytology (FNABC) for dilated ducts may be performed. Any intraductal proliferative lesions, if correctly sampled, may show abundant, three-dimensional epithelial cell nests[45]. Our experiences revealed that the diagnostic accuracy of DCIS was 62.5%, lower than that of invasive ductal carcinomas (more than 80%)[46]. The cytological diagnosis of atypical hyperplasia is much more difficult, because most are small (less than 2 mm) and require sampling of the appropriate cells[17]. Some authors used the grading/scoring system for benign and malignant intraductal proliferative lesions[47, 48]. The author would like to recommend that if the dilated ductal lesion can be detected by ultrasound, US-guided FNABC may be performed, however, if the lesion is mammographically calcified and thought to be an intraductal lesion, CNB is recommended[49].

Pathological Factors of DCIS other than Grading, and their Significance

In addition to the methods for evaluating and grading DCIS, the extent of the lesions (size) and the surgical margins (if breast conserving surgery is performed) should be described. The Van Nuys

Prognostic Index (VNPI), which is the sum of grade, extent, and margin status, correlates well with the risk for local recurrence[50]. However, the overall survival, at least 5- or 10-years later, were not significantly different. Additionally, the ratio of invasive recurrences among all recurrent cases (almost half of the cases, as in similar results in Japanese patients[51]) was not be influenced by the VNPI.

Other pathological parameters are detected by special techniques, but they are not always performed in routine practice. The Ki-67 index, hormone receptor status (ER/PgR), HER-2/neu status, and p53 expression status are shown in Table 4. Many articles have examined the overexpression of c-erbB-2 (HER-2/neu) in high-grade DCIS, and the frequency of overexpression was higher than that of invasive ductal carcinomas.

Finally, lymph node metastases of DCIS are reported in almost 0%, or 1-2% of the cases, as mentioned previously. The method of pathological examination, rather than underestimation of microinvasion, may be the cause of the unexpected metastasis. Most node positive DCISs are higher-grade lesions.

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Breast Conserving Surgery with Primary Volume Replacement using a Lateral Tissue Flap

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Breast conserving surgery (BCS) is now a standard surgical treatment for early breast cancer. The number of patients with tumors under 3 cm who underwent breast conserving surgery overtook the number of patients who underwent total mastectomy for the first time in Japan in 2003. We have been employing breast conserving surgery with primary reconstruction using a lateral tissue flap (LTF), and have performed breast conserving surgery for 266 patients from 1990 to 2002. The incidence of local relapse was 5.6%. Although we did not irradiate a low risk group of 101 patients, our method is not inferior to other reports in which all cases underwent irradiation. Primary reconstruction with LTF has three advantages. The first is that we can avoid poly-surgery for breast reconstruction. The second is that the volume of the graft is maintained longer than reconstruction with a musculo-cutaneous flap. The third is that patients can avoid allergic reactions or granulomas as seen with artificial prosthesies. In conclusion, breast conserving surgery with immediate volume replacement with a LTF is a reasonable surgical procedure and has the advantage of avoiding unnecessary surgical procedures for reconstruction and surgical invasion without delaying the diagnosis of local relapse. Moreover, an adequate assessment of risk can spare low risk groups irradiation.

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Key words: Breast conserving surgery, Lateral tissue flap

The incidence of breast cancer is the greatest of all female malignancies since 1991 and is still increasing in Japan. The mortality rate reached the third highest after lung cancer and gastric cancer in 1998. Patient demand helped develop breast conserving surgery (BCS) as a local treatment to maximize prognosis and cosmesis.

Breast conserving surgery was established as a standard surgical procedure in United States and Europe in the late 1980s[1]. The number of patients with breast cancer under 3 cm in size who underwent breast conserving surgery overtook the number of patients who was underwent total mastectomy in 2003 for the first time in Japan. The coexistence of good prognosis and cosmesis is the most important advantage of BCS. To achieve these two aims, we have started quadrantectomy (Bq) based on the anatomical structure of the mammary gland since 1990[2]. Compensating for the large volume defect generated by quadrantectomy was a problem. Quadrantectomy generally requires more breast volume be excised than partial mastectomy. We employed lateral tissue flap (LTF) reconstruction to compensate for the defect resulting from quadrantectomy. LTF is composed of adipose tissue placed caudal to the axillary arch.

Primary volume replacement for BCS has the risk of delaying the diagnosis of local recurrence. Since most of local recurrences occur within 5 years, intensive local examination and periodic observation is required. In this article, we describe the method for breast conserving surgery with immediate reconstruction with a LTF, and the clinical outcomes concerning local recurrence after breast conserving surgery with primary volume replacement using LTF.

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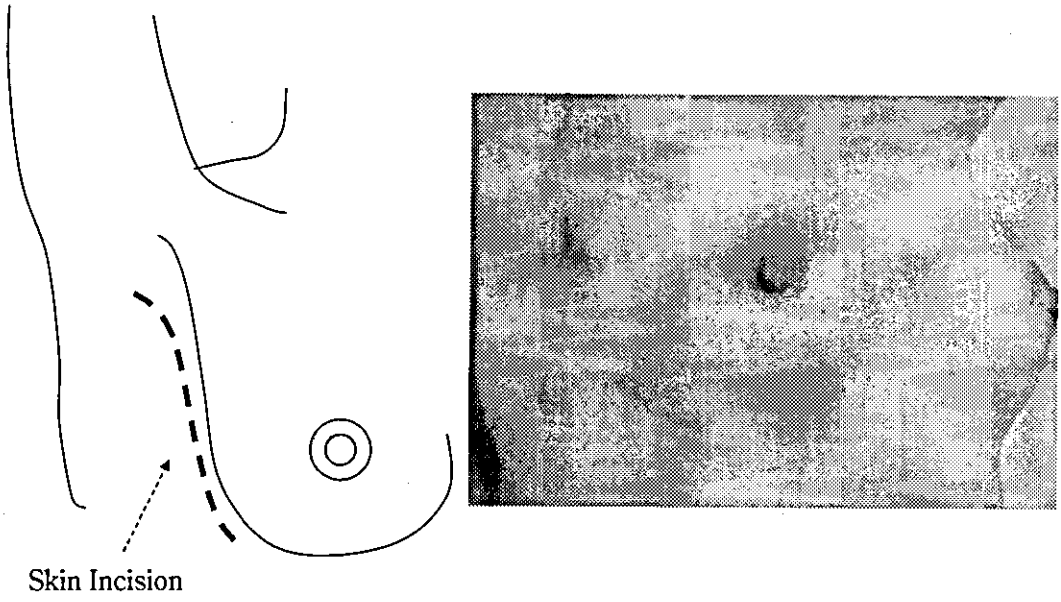

Fig 1. Lateral incision of breast conserving surgery.

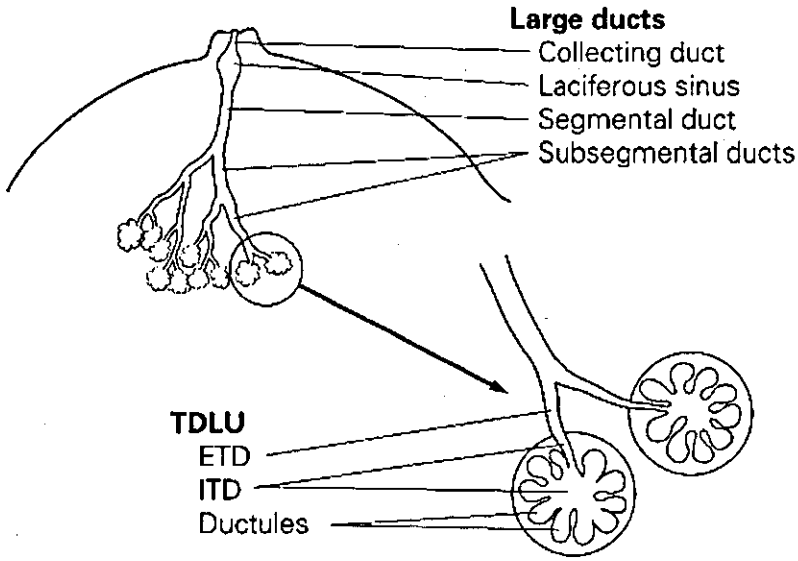

Fig 2. Duct-lobular system of the mammary gland.

Surgical Procedures

Skin Incision and Abrasion

In our surgical treatment of BCS, a sigmoid skin incision is made on the middle axillary line (lateral incision) to avoid an operative scar which can be seen from an anterior view (Fig 1). A lateral incision is made to excise tumors under 3 cm in diameter at any location to perform the quadrantectomy, volume replacement with LTF and axillary lymph node dissection.

The skin is widely peeled at the subcutaneous layer with a radio knife to allow quadrantectomy, axillary dissection and volume replacement with a single incision. Skin over the caudal area of the axillary region is also peeled back to make the LTF to correct the volume defect.

Quadrantectomy

We excise tumors using quadrantectomy for BCS. Quadrantectomy is performed based on the

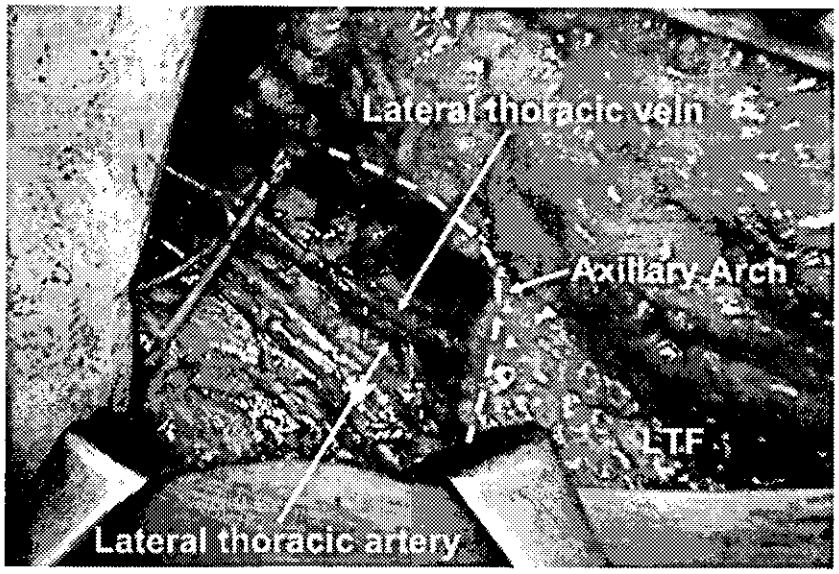

Fig 3. Lateral thoracic vein, axillary arch and the lateral tissue flap.

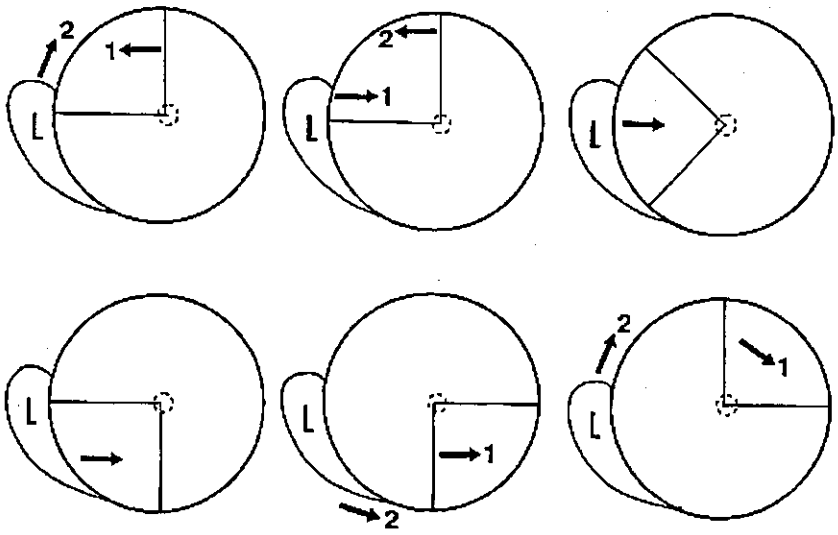

Fig 4. Rotation of the lateral tissue flap.

anatomical extension and structure of the duct-lobule system of the mammary gland to achieve complete resection of the tumor and its extension to the ductal structure (Fig 2)[2]. We perform partial mastectomy if there is no finding of tumor extension in the mammary duct. Tumor extension is evaluated by X-CT, MRI and ultrasonography.

Volume Replacement with LTF

LTF is made with adipose tissue located caudal to the axillary arch. The axillary arch is the caudal border of the axillary region, and is composed of connective tissue related to axillary fascia (Fig 3). The blood supply and drainage of the LTF is maintained by lateral thoracic vessels and communicating vessels from the latissimus dorsi. When we prepare the LTF, we preserve the communicating vessels from the latissimus dorsi and/or lateral thoracic vessels (Fig 3). To preserve these vessels is the key point to prevent necrosis of the LTF. Volume replacement is performed by rotation of the LTF. Indirect volume replacement is performed for medial volume defect in areas of A and B (Fig 4). Direct volume replacement is performed for lateral volume defect in areas of C and D (Fig 4).

Fig 5. Long-term anterior view of the breast after breast conserving surgery.

Irradiation Group and Non-irradiation Group

Irradiation of the conserved breast was performed for 165 patients. We avoided irradiation for 101 of patients at low risk of local recurrence. Low risk group was defined as pathologically n0, ly (− or 1+), without an extended intra-ductal component, with negative margins (cancer free within 5 mm of the surgical margin), without multi-centric lesions and without a contra-lateral lesion.

Incidence of Local Recurrence

We performed breast conserving surgery for 266 patients from Sep. 1990 to Dec. 2003. Fifteen patients (5.6%) had local relapse. The median observation period was 72 months. Irradation of the conserved breast was performed for 165 patients. We avoided irradiation for 101 low risk patients as noted above. In the non-irradiated patients the incidence of local relapse was 6.9%. The incidence of local relapse in the group undergoing irradiation was 4.8%. There was no statistically significant difference between irradiated and non-irradiated cases.

Cosmesis

Fig 5 shows the cosmetic features of BCT with volume replacement using LTF for the right breast. There is no conspicuous difference between either the breast. The operation scar is not seen from the front.

Discussion

We started breast conserving surgery in 1989. One of the advantages of using LTF for volume replacement is long-term maintenance of the graft. LTF does not shrink like a musculo-cutaneous flap (MC flap) using the latissimus dorsi, which shrinks because of disuse atrophy.

Volume replacement with LTF is a minimally invasive breast reconstruction technique compared with breast reconstruction with a saline bag.

The incidence of local recurrence is not inferior to that of ordinary breast conserving surgery. In our department, local recurrence is found in early stages without distant metastasis in almost all cases by careful and frequent follow up by mammography and ultrasonography. For most patients, local recurrence occurs within 5 years, we perform ultrasonography every 3-6 months for 5 years. Annual examination by mammography is also performed. The incidence of local recurrence is 5.6%. This is not inferior to the incidence reported in western countries[1, 6-9]. This is due to volume resection of the mammary gland sufficient to achieve negative margins and appropriate irradiation after estimation of risk. As Voogd *et al.* reported that an age younger than 35 years, extended intra-ductal component, and vascular invasion are the factors that contribute to local recurrence[10], our data suggests that appropriate risk evaluation can avoid irradiation in the low-risk group. On the other hand, local recurrence in high-risk cases with is well controlled by irradiation. We were able to reduce the rate of local relapse to as low as 4.8%. Recently, we estimated tumor extension by CT and MRI[3, 4]. When there is very limited extent of tumor, we employ partial mastectomy. These modalities also assist us in improving negative margin rates.

With breast conserving surgery followed by volume replacement with LTF, blood flow of the LTF should be well maintained. We preserve communicating branches from the latissimus dorsi and lateral thoracic vessels when we prepare the LTF. Careful lymph node dissection should be done with complete removal of lymph nodes and adipose tissue around the lateral thoracic vessels when we preserve lateral thoracic vessels so as to completely remove cancer cells (Fig 3).

The long term volume stability of the LTF is good, because adipose tissue does not shrink due