Original Article

Clinicopathological Characteristics of Invasive Lobular Carcinoma of the Breast

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BACKGROUND: The clinical features of invasive lobular carcinoma (ILC) of the breast have remained unclear due to the rarity of such cases. This study investigated the clinical and pathological features of ILC.

METHODS: The medical records of 413 patients with invasive breast cancer who underwent surgery in our department were reviewed. These cases included 13 patients with ILC (3.1%).

RESULTS: The age of the patients ranged from 36 to 77 years old (mean, 56). The tumour size was evaluated as T1 in five patients, T2–4 in 8. The lymph node metastasis was diagnosed as negative in six patients, positive in six. In this patient population, 11 (85%) and nine (69%) patients were positive for oestrogen and progesterone receptors, respectively. The 5-year survival rate was 76.2%, which was not significantly different from other types of invasive breast cancer. Extensive intraperitoneal metastasis was observed in two of the three patients. Two patients had bilateral carcinoma and one patient had a multicentric lesion in the ipsilateral breast.

CONCLUSION: Multicentric development of breast cancer and intraperitoneal metastasis were one of clinical characteristics of ILC. The prognosis of ILC was not significantly different from other types of invasive breast carcinoma. [*Asian J Surg* 2009;32(2):76–80]

Key Words: breast cancer; intraperitoneal metastasis, invasive lobular carcinoma, prognosis, surgical resection

Introduction

Breast cancer is the one of leading causes of cancer death among women in industrialized countries.[1] In 1941, Stewart et al. proposed the entity of lobular carcinoma as a type of breast cancer.[2] They described both an invasive form and an *in situ* form of the disease which was confined to the lobule and terminal ducts.[3] Invasive lobular carcinoma (ILC) is the second most common type of invasive breast cancer after invasive ductal carcinoma, and accounts for 5–15% of all breast cancer in Europe and the United States, respectively.[4,5] The incidence of invasive lobular carcinoma in Japan was approximately 1–4% among all breast cancer.[6,7] A recent epidemic study indicated that the incidence of this type of breast cancer is increasing, especially among postmenopausal women.[6] Reports indicated that the use of combined oestrogen and progesterone hormone replacement therapy increased the risk of all types of breast cancer, especially ILC.[5]

Because ILC lesions are less common and include several subtypes such as, classic, alveolar, solid, tubulo-lobular, signet ring cell and pleomorphic subtypes,[8] it is somewhat difficult to describe the clinical characteristics categorically. However, some of the clinical features have been

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reported to be (1) multicentric development in the same or the adjacent breast in greater proportions than other types of breast cancer, (2) ill-defined margins and subtle thickening or indurations observed in mammography (finding of architectural distortion), (3) more frequent expression of oestrogen receptors (ER) and (4) gastrointestinal and peritoneal metastasis.[6,8–10] Although there are several differences in the clinicopathological characteristics of ILC and invasive ductal carcinoma, both types of carcinoma are usually managed using the same clinical strategy. In this study, the clinical and pathological characteristics of patients with invasive lobular carcinoma who underwent surgery in this department were reviewed.

Patients and methods

The clinical and pathological features of 413 patients with invasive breast cancer who underwent a surgical resection in this department between 1981 and 2005 were observed. The patients' records were retrieved and the clinical data, preoperative examination results, details of the surgical procedure, histopathological findings, and TNM stages of all patients were reviewed. All patients had received a physical examination, ultrasonography of the breast, and mammography during the preoperative evaluation. The assessments for distant metastasis included chest roentgenography, computed tomography (CT) of the chest and upper abdomen, and bone scintigraphy. All resected specimens, including the primary tumour and resected regional lymph nodes were examined for tumour histology and the extent of lymph node metastases. The histopathological findings were classified according to the General Rules for Clinical and Pathological Recording of Breast Cancer 2005.[11] ER and progesterone receptor (PgR) in the cancer tissues were measured by an enzyme immunoassay, or immunohistochemical staining of sections taken from formalin-fixed, paraffin-embedded blocks of the surgical specimens. The cancer tissues were available in 312 patients (75.5%) for evaluation of hormone receptors. Follow-up information was obtained from all patients through office visits or telephone interviews with either the patient, a relative, or their primary physicians. The mean observation time was 4.6 years.

Categorical variables were compared by Fisher's exact test for proportion. The survival curve was calculated by the Kaplan-Meier method, and compared by using the Log-rank test for univariate analysis. Differences were considered to be significant, if the *p* value was less than 0.05. The Statview V software program (Abacus Concept, Berkeley, CA) was used for all statistical analyses.

Results

The average age of the patients was 56.3 years (range, 36–77 years) and 53.5 (range, 23–97 years old) in the patients with ILC and other types of invasive breast cancer, respectively. The subjects included 13 patients with ILC (3.1%) among the 413 patients with invasive breast cancer. They consisted of five premenopausal and eight postmenopausal women. The tumour size of the ILC was evaluated as T1 in five patients, T2 in six, T3 in one and T4 in one (Table 1). The proportion of T1 tumours was similar to that of other types of invasive breast cancer. The lymph node metastasis of the ILC patients was diagnosed pathologically as N0 in six patients, N1 in four, N2 in two, and N3 in one. The percentage of lymph node metastasis tended to be higher than that of other types of invasive breast cancer, but no statistical significant difference was observed. The surgical procedure used for patients with ILC included Bt + Ax in six patients, Bt + Ax + Ic in two, Bt + Ax + Ic + Mn in two, Bt in two and Bt + Ax + Ic + Mn + Mj in one. In these cases, 11 (85%) and nine (69%) patients with ILC were positive for ER and PgR, respectively. Adjuvant chemotherapy was administered in 10 patients based on the following regimen; CAF (cyclophosphamide + adriamycin + fluorouracil) in five, AC (cyclophosphamide + adriamycin) followed by paclitaxel in three, 5′DFUR (5′-deoxy-5-fluorouridine) in two patients. Endocrine therapy with tamoxifen was combined in three patients, and aromatase inhibitor was administrated in two. An oophorectomy was performed in two patients in the 1980s. The 5-year survival rate was 76.2%, which was not significantly different from that of patients with other types of invasive breast cancer (Figure 1). In two of the three patients who died, extensive intraperitoneal metastases were detected. Two patients had bilateral lobular carcinoma (one synchronous and one metachronous) and one patient had a multicentric lesion in the ipsilateral breast.

Discussion

ILC develops from the acinar epithelium of the mammary gland and frequently invades the normal tissues without involvement of the abundant desmoplastic response that

Table 1. Comparison of the pathological characteristics between invasive lobular carcinoma and other types of invasive breast cancers

| Characteristics	Invasive lobular carcinoma (n = 13)	Other types of invasive breast cancer (n = 400)
	Number of patients (%)	Number of patients (%)
T categories		
T1	5 (38.5)	168 (42.0)
T2	6 (46.2)	172 (43.0)
T3	1 (7.7)	51 (12.8)
T4	1 (7.7)	9 (2.3)
N categories		
N0	6 (46.2)	241 (61.5)
N1	4 (30.8)	117 (29.8)
N2	2 (15.4)	26 (6.6)
N3	1 (7.7)	8 (2.0)
M categories		
M0	10 (76.9)	386 (96.5)
M1	3 (23.1)	14 (3.5)
Oestrogen receptor status		
Positive	11 (84.6)	199 (63.8)
Negative	2 (15.4)	113 (36.2)
Progesterone receptor status		
Positive	9 (69.2)	165 (52.9)
Negative	4 (30.8)	147 (47.1)
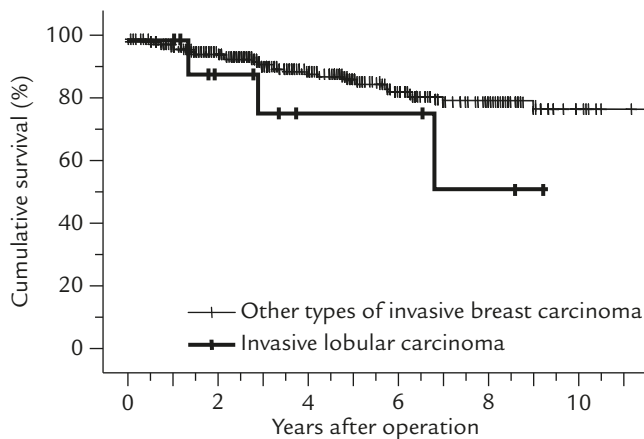
Figure 1. Overall survival curves of the patients with breast cancer. The 5-year survival rate of patients with invasive lobular carcinoma was 76.2% which was not significantly different from that of patients with other types of invasive breast cancer.

usually accompanies invasive ductal carcinoma.[2,3] Focal masses are not always obvious clinical features, but they are sometimes difficult to distinguish from dense normal parenchyma.[4] More than one third of mammograms of these lesions reveal vague asymmetries, poorly defined opacities, or architectural distortions.[8] Microcalcifications are frequent manifestations of ductal carcinomas, but are uncommon in ILC.[12] Using sonography, ILC appears as a heterogeneous, hypoechoic mass with ill-defined margins and a posterior acoustic shadow.[13] Selinko et al reported that sonography had a greater sensitivity than mammography for the detection of ILC and had the advantage of evaluating the presence of the axillary lymph node metastasis.[14] However, the sensitivity in the detection of ILC has varied according to the investigations, ranging from 57–81% for mammography and 68–87% for sonography.[13,15] Enhanced magnetic resonance (MR) imaging of the breast is extremely sensitive for the detection of ILC and is also useful to evaluate the extent of the disease.[16] Rodenko et al reported that the extent of disease determined by pathological examination correlated well with the prediction based on MR imaging.[17] The ill-defined margins are probably related to the pathological findings that ILC spreads through the breast parenchyma with diffuse infiltration of single rows of malignant cells in a linear fashion surrounding the non neoplastic ducts

and that this infiltration causes little disruption of the underlying anatomical structures and generates only a slight surrounding connective tissue reaction.[18]

Because of the infiltrative growth pattern and frequent discontinuity (multicentric development) that is observed in ILC, there has been a tendency to treat patients with more aggressive surgery, including mastectomy and standard axillary lymph node dissection. The rate of local recurrence after conservative surgery and radiation therapy is high because of the frequent incidence of multicentricity and bilateral occurrence.[19,20] The rate of positive margin in the breast conservation therapy for ILC is reported to be over 50% and it is more frequent than that observed in invasive ductal carcinoma.[21–23] In the present study, none of the patients underwent breast conservation therapy. Vo et al reported the result of with breast conservation therapy (BCT) and radiation in 84 patients with ILC and 1,126 with invasive ductal carcinoma with stage I or II disease. In their study, the 10-year local-regional recurrence rates for the ILC group and invasive ductal carcinoma group were 7% and 9%, respectively, indicating no significant differences between the two groups.[24] Therefore, breast conservation treatment is now being increasingly used for invasive lobular carcinoma, yielding outcomes equivalent to those of more aggressive surgical treatment.[25,26] Santiago et al also reported that similar long-term results for breast conservation treatment for invasive lobular carcinoma to that observed with invasive ductal carcinoma.[27] Therefore, we considered that breast conservation treatment should have been tried for patients at stage I (T1) in this study. The response to primary chemotherapy for ILC is lower than invasive ductal carcinoma; therefore systemic therapy should be restricted to patients with inoperable or recurrent ILC.[28] Although adjuvant chemotherapy in breast cancer patients presenting with lymph nodal involvement is a standard option currently, it is necessary to consider a prospective randomized trial to evaluate the role of adjuvant chemotherapy versus hormonal therapy in ILC patients.[29]

The tumour diameter observed in ILC is reported to be slightly larger in comparison to other types of invasive breast cancer.[10] However the proportion of T1 was similar to other invasive carcinomas in this study. The incidence of lymph node metastasis with ILC tended to be higher (53.8%) than that of other types of invasive breast cancer (38.5%) in this study, but the difference was not statistically significant. The proportion of lymph node metastasis of ILC is reported to occur at the same rate in comparison to other types of invasive breast cancer.[10] ER expression was reported to reveal more frequently in ILC than other types of invasive breast cancer.[30] In the cases reviewed in this study, 85% of the ILC patients were positive for ER which was a higher ratio than other types of invasive breast cancer.

The pattern of distant metastasis in ILC was different from invasive ductal cancer of the breast. Lung and pleura involvement was more frequently observed with invasive ductal carcinoma, as was involvement of the distant lymph nodes and of the central nervous system. The metastasis of the gastrointestinal tract, gynaecologic organs or the peritoneum is rare in invasive ductal carcinoma. On the other hand, ILC often metastasizes to the intraperitoneal organs (through haematogenous metastasis and peritoneal dissemination), suggesting that this type of metastasis is one of the specific features of ILC.[31–33] Metastasis of ILC origin in the intraperitoneal organs frequently shows a signet ring cell appearance and the loss of expression of membrane E-cadherine.[34] In this study, two patients died due to extensive intraperitoneal metastasis (mural haematogenous metastases of gastrointestinal tract). In spite of these clinicopathological differences, the prognosis of ILC shows no difference in comparison with other types of invasive breast cancer.[10,30]

The multicentric development of the ipsilateral or bilateral breast is another clinical feature of ILC. Bilateral involvement is reported to be 20–29% in ILC, which is an extremely high frequency as compared with that of invasive ductal carcinoma.[19,20,35] This finding suggests that careful follow-up is necessary for development of a metachronous contralateral carcinoma after surgery. This study included two patients with bilateral lobular carcinoma of the breast. One patient presented with synchronous cancer and the other patients was diagnosed with a contralateral bilateral lobular carcinoma 5 years after initial operation.

In conclusion, there are several clinicopathological characteristics of ILC, however, the prognosis of ILC is not significantly different from other types of invasive breast carcinoma and therefore no differences in the therapeutic management are considered to be necessary.

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