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Original Article

Mucinous Carcinoma of the Breast: Clinicopathological Features and Long-term Prognosis in Comparison with Invasive Ductal Cancer; A Single Hospital's 30+-Year Experience

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Mucinous carcinoma (MC) of the breast is a rare and special type of malignancy, with a substantial amount of extracellular mucin. We compared the clinicopathological features and the long-term survival of MC patients with those of invasive ductal carcinoma-no special type (IDC-NST) patients, and we examined prognostic factors of MC. A total of 116 patients with mucinous carcinoma and 3,258 patients with IDC-NST who underwent surgery at our hospital (1977-2008) were enrolled. The 10-year overall survival rate and breast cancer-specific survival rate (BSS) of the MC patients (88.3%, 93.7%) were both significantly higher than those of IDC-NST patients (81.6%, 85.0%) ($p=0.015$, $p=0.005$, respectively). A Cox regression analysis demonstrated that MC tended to be an independent prognostic factor (hazard ratio 0.44, $p=0.098$). The BSS of the MC patients with positive lymph node (LN) metastasis was significantly poorer than that of the patients without it, by univariate analysis ($p=0.002$). The tumor size in the MC patients with positive LN metastasis (mean 3.2 cm) was significantly larger than that in the patients without it (mean 1.9 cm) ($p=0.0004$). Although a Cox regression analysis revealed no independent factor, MC patients with positive LN metastasis should be treated for advanced invasive ductal breast cancer.

Key words: breast cancer, mucinous carcinoma, clinicopathological features, long-term prognosis

Mucinous carcinoma (MC) of the breast is a rare and special type of malignancy with a substantial amount of extracellular mucin. The incidence of MC is 1-6% of all breast malignancies, and the prognosis of the patients with MC is reported to be better than that of patients with invasive ductal cancer-no special type (IDC-NST) [1-3]. MC patients were also reported to tend to be elderly, menopausal, and have a high expression of hormone receptors and a low expression of human epidermal growth factor receptor 2 (HER2). MC is defined as having a mucinous component comprising >50% of the lesion. MC is divided into 2 groups, a pure type and a mixed type, according to the presence of a concomitant area with typical infiltrating ductal carcinoma or the proportion of mucin; however, a clear definition has not been established [1-6].

A large number of MC patients were analyzed using the Surveillance, Epidemiology and End Results (SEER) database, and these analyses revealed prognostic factors of MC patients [7, 8]. However, the long-term prognosis of MC patients in Japan has not been fully clarified. We conducted the present study determine whether the previously reported characteristics of MC patients can be applied to Japanese patients who underwent surgery during a >30-year period at a single hospital. We inves-

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tigated the long-term prognoses of these MC patients in a comparison with those of IDC-NST patients, and we sought to identify prognostic factors for MC patients.

Patients and Methods

Of the 4,654 patients who underwent breast surgery at Oomoto Hospital (No. 0111442, a medical corporation hospital in Okayama, Japan) between February 1977 and December 2008, 116 patients with MC and 3,258 patients with IDC-NST were enrolled in this study. The IDC-NST group consisted of 1,003 cases of the tubule-forming type, 1,045 cases of the solid type, and 1,210 cases of the scirrhous type according to the General Rules for Clinical and Pathological Recording of Breast Cancer issued by the Japanese Breast Cancer Society [9]. Patients with prior or simultaneous cancer of other organs or other breast cancer (ipsilateral or opposite breast) were excluded.

The clinicopathological factors of the MC group were evaluated in a comparison with those of the IDC-NST patients. The patients' mammography (MG) findings and ultrasonography (US) findings were categorized based on the Breast Imaging-Reporting and Data System (BI-RADS) [10]. The tumor stages were classified based on the TNM (UICC) classification [11]. Long-term prognoses were examined in 80 patients with MC and 2,813 patients with IDC-NST whose follow-up periods after surgery were > 5 years. We compared the overall survival (OS) rate and the breast cancer-specific survival (BSS) rate of the MC group with those of the IDC-NST group. The BSS of the MC patients was evaluated in relation to their lymph node (LN) metastasis and tumor sizes. Patients with recurrence of MC were investigated in detail. Prognostic factors for invasive ductal carcinoma (MC+IDC-NST) and MC were evaluated by a multivariate analysis (Cox regression).

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [12]. More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics. The two patient groups' OS curves and the BSS curves were determined and plotted by the Kaplan-Meier method. In general, p-values < 0.05 by Fisher's exact test, the unpaired t-test, log rank test, and Cox regression proportional hazards model were considered significant.

This study was approved by the Ethics Committee of Oomoto Hospital in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions.

Results

The incidence of mucinous carcinoma was 3.43% of all of the invasive ductal cancers in this patient series during the study period. The clinicopathological factors of the MC and IDC-NST groups are summarized in Table 1. The MC patients (mean age 56.8 years old) were significantly older than the IDC-NST patients (mean age 54.0 years old). The preoperative BI-RADS values of MG and US for malignancy of the MC cases were both significantly lower than those of the IDC-NST cases ($p = 0.001$, $p < 0.001$). Breast-conserving surgery was performed more frequently for the MC patients than for the IDC-NST patients ($p = 0.006$). The rate of positive LN metastasis in the MC group (15.2%) was significantly lower than that in the IDC-NST group (39.2%) ($p < 0.001$). There were no significant differences in tumor size between the MC and IDC-NST patients.

The rate of positive estrogen receptor (ER) in the MC patients (81.7%) was significantly higher than that in the IDC-NST patients (68.2%) ($p = 0.002$). Chemotherapy was performed less frequently for the MC patients than for the IDH-NST patients. The rate of radiation treatment rate in the total patient series was very low, because our hospital did not recommend radiation treatment for most of the patients who undergo margin-negative breast-conserving surgery in this cohort series until the General Rules for Clinical and Pathological Recording of Breast Cancer were issued in 2005.

The OS and BSS of the MC and IDC-NST patients. The 10-year OS (88.3%) of the MC patients was significantly higher than that of the IDC-NST patients (81.6%) ($p = 0.0148$) (Fig. 1). As illustrated in Fig. 2, the 10-year BSS of the MC patients (93.7%) was significantly higher than that of the IDC-NST patients (85.0%) ($p = 0.00488$). The Cox regression proportional hazards model for BSS (MC+IDC-NST) revealed that tumor size and positive LN metastasis were strong independent prognostic factors (Table 2). MC was an inde-

pendent factor, although not significantly (hazard ratio [HR] 0.44, $p=0.098$).

The BSS of the MC patients in relation to the clinical factors. Of the 80 MC patients, 9 died (breast cancer, n=4; other disease, n=5). The characteristics of the 4 MC patients with recurrence (1 local and 3 distant) are shown in Table 3. All 4 of these patients had lymphovascular invasion, and 3 of them had positive LN metastasis.

The BSS of the MC patients with positive LN metas-

Table 1 Clinicopathological factors of MC and IDC-NST

Factor	Group	MC	IDC-NST	*p*-value
n		116	3,258	
Age	Mean (SD) Years	56.79 (15.71)	53.98 (12.14)	0.015
	Median Years	56	53	
Menopause (%)	No	46 (39.7)	1,453 (44.6)	
	Yes	70 (60.3)	1,805 (55.4)	0.298
Side (%)	Left	62 (53.4)	1,753 (53.8)	1
	Right	54 (46.6)	1,505 (46.2)	
Subsites (%)	1. Nipple	9 (7.8)	181 (5.6)	NA
	2. Central portion	1 (0.9)	156 (4.8)	
	3. Upper-inner quadrant	41 (35.3)	948 (29.1)	
	4. Lower-outer quadrant	11 (9.5)	205 (6.3)	
	5. Upper-outer quadrant	45 (38.8)	1,473 (45.2)	
	6. Lower-outer quadrant	9 (7.8)	295 (9.1)	
BI-RADS MG category (%)	2,3,4	28 (26.4)	436 (14.0)	0.001
	5	78 (73.6)	2,676 (86.0)	
BI-RADS US category (%)	2,3,4	38 (34.9)	445 (14.7)	<0.001
	5	71 (65.1)	2,584 (85.3)	
Operative procedure (%)	Breast conserving surgery	46 (39.7)	897 (27.5)	0.006
	Mastectomy	70 (60.3)	2,361 (72.5)	
Positive LN (%)	No	84 (84.8)	1,884 (60.8)	<0.001
	Yes	15 (15.2)	1,217 (39.2)	
Number of positive LN	Mean (sd) Number	2.80 (1.90)	6.97 (9.29)	0.083
Tumor size (%)	<2 cm	62 (53.4)	1,654 (51.2)	0.706
	$\geqq 2$ cm	54 (46.6)	1,576 (48.8)	
Tumor size	Mean (sd) cm	2.05 (1.30)	2.34 (1.94)	0.11
TNM stage (%)	I	77 (66.4)	2,094 (64.3)	<0.001
	II	18 (15.5)	646 (19.8)	
	III	3 (2.6)	276 (8.5)	
	IV	0 (0.0)	81 (2.5)	
	Unknown	18 (15.5)	161 (4.9)	
ER (%)	Negative	20 (18.3)	974 (31.8)	0.002
	Positive	89 (81.7)	2,089 (68.2)	
PgR (%)	Negative	35 (32.1)	1,303 (43.4)	0.023
	Positive	74 (67.9)	1,702 (56.6)	
Hormone therapy (%)	No	45 (38.8)	1,244 (38.2)	0.923
	Yes	71 (61.2)	2,014 (61.8)	
HER2 (%)	Negative	31 (96.9)	597 (86.1)	0.108
	Positive	1 (3.1)	96 (13.9)	
Chemotherapy (%)	No	47 (40.5)	587 (18.0)	<0.001
	Yes	69 (59.5)	2,671 (82.0)	
Radiation (%)	No	115 (99.1)	3,197 (98.1)	0.724
	Yes	1 (0.9)	61 (1.9)	

MC, mucinous carcinoma; IDC-NST, invasive mucinous carcinoma of no special type; BI-RADS, breast imaging-reporting and data system; MG, mammography; US, ultrasound; LN, lymph node; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor 2; NA, not applicable.

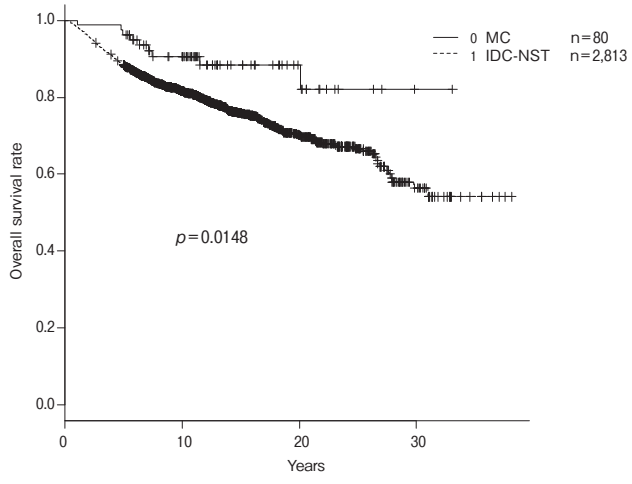

Fig. 1 The overall survival (OS) rates of the MC and IDC-NST groups.

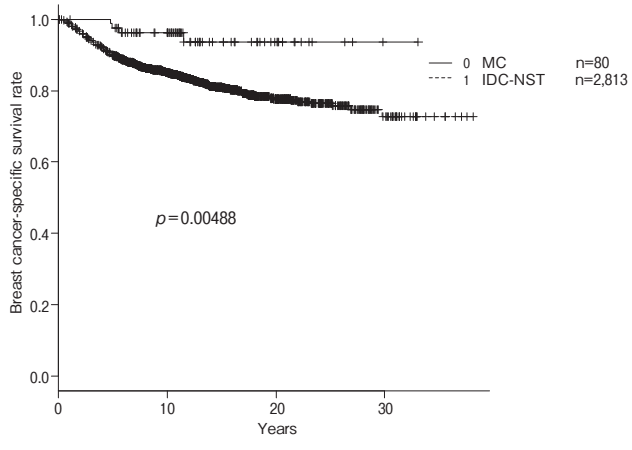

Fig. 2 The breast cancer-specific survival (BSS) rates of the MC and IDC-NST groups.

Table 2 Cox regression proportional hazards ratio of breast cancer-specific survival (IDC-NST+MC)

Factor	Hazard ratio	*p*-value
Tumor size of 2 cm or more	2.27 (1.84–2.80)	2.11E–14
Positive lymph node metastasis	4.83 (3.85–6.05)	0
Hormone therapy	1.09 (0.89–1.34)	0.4
Chemotherapy	1.17 (0.79–1.66)	0.38
MC vs IDC-NST	0.44 (0.16–1.17)	0.098

MC, mucinous carcinoma; IDC-NST, invasive mucinous carcinoma of no special type.

Table 3 Characteristics of 4 patients with local and/or distant recurrence

Patient (Female)	Age (Breast cancer detected)	Tumor size (cm)	LVI	Receptor status	Lymph node involvement (Number of positive nodes)	Treatment	Type of recurrence	Time to recurrence (year)	Overall survical period (year)
1	47 years old	1.5	Yes	ER negative, PgR negative	Positive (5)	Mastectomy/ALND, chemotherapy, endocrine therapy	Ipsilateral side axilla, neck	4.7	5.5
2	43 years old	7	Yes	ER positive, PgR positive	Negative	Mastectomy/ALND, chemotherapy, endocrine therapy	Distant (ovarium)	3.2	4.9
3	47 years old	4	Yes	ER positive, PgR positive	Positive (8)	Mastectomy/ALND, chemotherapy, endocrine therapy	Distant (brain)	6.0	11.5
4	46 years old	2.5	Yes	ER negative, PgR positive	Positive (2)	Mastectomy/ALND, chemotherapy, endocrine therapy	Distant (lung)	3.0	4.8

LVI, lymphovascular invasion; ALND, axillary lymph node dissection.

tasis was significantly lower than that of the MC patients without it ($p=0.0018$) (Fig. 3). The BSS of the MC patients with a tumor size ≥2 cm was lower than that of the MC patients with smaller tumor sizes, but the difference was not significant ($p=0.156$) (Fig. 4). Among the MC patients, the tumor size (3.2±1.7 cm, mean±SD) in the patients with positive LN metastasis was significantly larger than the tumor size of the patients without positive LN metastasis (1.9±1.2 cm, mean±SD) ($p=0.0004$) (Fig. 5). The Cox regression proportional hazards model revealed no independent factor for BSS in the patients with MC in this series (Table 4).

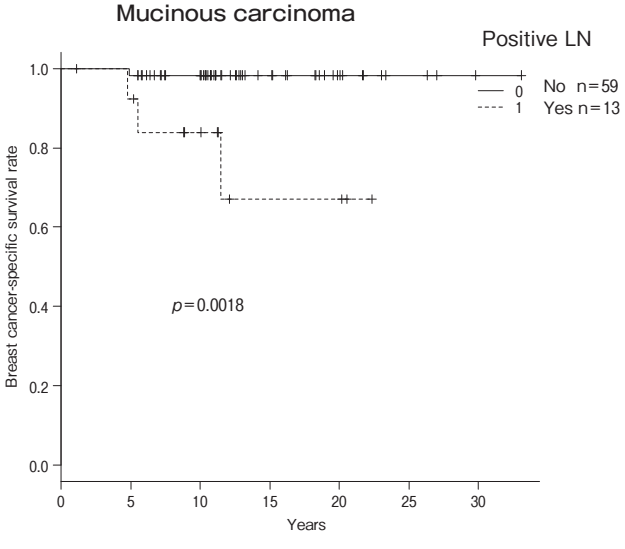

Fig. 3 The BSS of the MC patients according to positivity of lymph node metastasis.

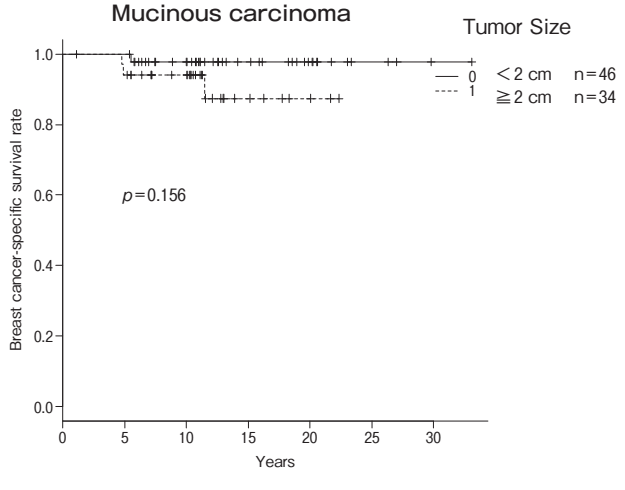

Fig. 4 The BSS of the MC patients according to tumor size.

Discussion

The results of our analyses demonstrated the following: Regarding IDC, (1) the OS and the BSS of the MC patients were significantly longer than those of the IDC-NST patients, and (2) MC tended to be an independent prognostic factor (HR 0.44, $p=0.098$). Among the MC patients, (1) the BSS of the patients with positive LN metastasis was significantly poorer than the BSS of the patients without positive LN metastasis; (2) The tumor size (mean 3.2 cm) in the MC patients with positive LN metastasis was significantly larger than that in the patients without positive LN metastasis (mean 1.9 cm) ($p=0.0004$); and (3) No independent prognostic factor was found for MC patients by Cox regression

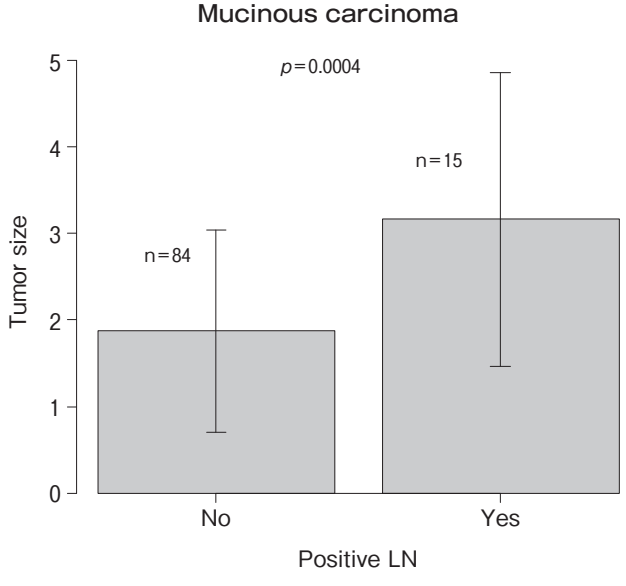

Fig. 5 Tumor size in relation to positivity of lymph node metastasis.

Table 4 Cox regression proportional hazards ratio of breast cancer-specific survival (MC)

Factor	Hazard ratio	*p*-value
Tumor size of 2 cm or more	3.22 (0.31–32.00)	0.33
Positive lymph node metastasis	2.61 (0.22–30.68)	0.24
Hormone therapy	168000000.00 (0.00–Inf)	1
Chemotherapy	122000000.00 (0.00–Inf)	1

MC, mucinous carcinoma.

analysis in this series.

The clinicopathological characteristics of the MC patients in this study were consistent with those previously reported. Compared to the present IDC-NST patients, the MC patients were older, had a more difficult preoperative diagnosis of malignancy, a lower rate of positive LN, and high positivity for hormone receptors. Among these factors, the reported median age of patients with MC has differed among countries, for unknown reasons. In the SEER database of the U.S., the MC patients (age range 68-75 years) were older than the IDC patients (61-53 years) [7, 8], whereas in Korea, the MC patients were younger (44-45 years) than the IDC patients (47 years) [13, 14]. In the present study, the MC patients (mean age 56 years) were older than the IDC-NST patients (mean age 53 years), but the age difference was smaller than that reported in the U.S.

Regarding the survival rates of MC patients, in our series at a single hospital in Japan, both the 10-year OS (88.3%) and the BSS (93.7%) of the 80 MC patients treated during the years 1977-2008 were significantly higher than those of the IDC-NST patients (81.6%, $p=0.015$; 85.0%, $p=0.005$, respectively). In 2008, Di Salverio *et al.* [7] used the SEER database and observed that the 10-year BSS of 11,400 patients with pure mucinous breast carcinoma (PMBC) treated during the years 1973-2002 (89%) was significantly higher than that of the IDC patients (72%), but there was no significant difference between these groups in OS. Fu *et al.* used [9] the SEER database and the using Life-Table method in 2016, and they reported that the 10-year cancer-specific survival rate (CSS) of 3,042 patients with mucinous breast cancer (MBC) who were treated in 1990-2007 (96%) was significantly higher than that of the IDC patients (85%). In 2010 in Korea, Park *et al.* [14] reported that the 10-year OS of 104 MC patients treated in 1986-2006 (86.3%) was significantly higher than that of the patients with IDC-NOS (not otherwise specified) (74.9%). Thus, although the OS and the BSS of MC and IDC-NST patients differed by the period in the above three studies, the MC patients had better prognoses compared to IDC-NST patients.

Regarding the prognostic factors of the invasive ductal cancer (MC+IDC-NST) patients in the present study, the Cox regression proportional hazards model revealed that positive LN metastasis and tumor size were strong independent prognostic factors. MC was also an independent better-prognosis factor, although not significantly (HR 0.44, $p=0.098$). In a large series from the SEER database, MC was an independent factor for better prognosis based on univariate and multivariate analyses [8]. Thus, MC is a positive independent prognostic factor in larger series of patients with invasive ductal cancer.

In the present study, 88% of the MC patients had a palpable mass. The frequency of the diagnosis of malignancy based on MG and US was lower in the MC patients compared to the IDC-NST patients. On MG, pure MC often presents as a circumscribed lesion [15, 16]. On US, the cystic appearance of MC may make it difficult to determine malignancy.

Regarding the prognostic factors of MC patients in the present study, the univariate analysis revealed that the BSS of the MC patients with positive LN metastasis was significantly poorer than the BSS of those without LN metastasis. However, the Cox proportional hazards model did not identify predictive factors for the MC patients. Of the 80 patients with MC, only four patients died of breast cancer. One reason for the insufficient information from the Cox proportional hazards model is that the incidence of events was and the total number of MC patients was small. The multivariate analysis of a large SEER series demonstrated that positive LN metastasis, poor differentiation, patient age, and tumor size are independent factors of a poor prognosis in MC patients [7, 8].

In the present series, 15% of the MC patients had positive LN metastasis, and the mean tumor size of the MC patients with positive LN metastasis (3.2 cm) was significantly larger than that of the MC patient without it (1.9 cm). Using a large contemporary multicenter series (111 MC patients, 1997-2004), Barkley *et al.* [4] reported that (1) 13% of the MC patients had positive LN metastasis, and (2) node positivity was associated with larger tumor size; the patients with positive LN metastasis had a significantly larger mean tumor size (2.7 cm) compared to that of the patients without LN metastasis (1.5 cm). Their results are consistent with ours. Thus, the size of the tumor is closely correlated with LN metastasis even for MC, which has a substantial amount of extracellular mucin. Consequently, the axillary nodal status in MC patients with larger tumors should be carefully investigated.

This study has several limitations. First, we were unable to separate the MC cases by subtype into "pure" or "mixed" based on pathology because the slides

obtained at our hospital from before 2002 were destroyed in the 2002 Tottori western earthquake. We used the breast cancer database of Oomoto Hospital and pathological reports; for all 4 patients who died of recurrence, we performed a re-excision from a paraffin block of the tumor tissue, and a pathologist confirmed the tumor to be mucinous carcinoma. A second limitation is that the number of MC patients (n = 80) was too small for the identification of definite prognostic predictors. A meta-analysis should be performed to evaluate this disease in Japanese patients.

In conclusion, the prognoses of the MC patients were significantly better than those of the IDC-NST patients. The MC patients with positive LN metastasis had significantly poorer prognoses compared to those without positive LN metastasis. The tumor sizes of the MC patients with positive LN metastasis were significantly larger than those of the MC patients without LN metastasis. Although our Cox regression analysis revealed no independent factors, MC patients with positive LN metastasis should be treated for advanced invasive ductal breast cancer.

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