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Histopathologic and Immunohistochemical Analysis of Pure Type Mucinous Carcinomas of Breast

조선대학교 대학원

의학과

김 동 출

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순수형 유방점액암종의 조직학적 검토와
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이 논문을 의학박사학위 논문으로 제출함.

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ABSTRACT

Histopathologic and Immunohistochemical Analysis of Pure Type Mucinous Carcinomas of Breast

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Background: The mucinous carcinomas are known to be well-demarcated border with less aggressive biologic behavior and good prognosis. The aim of this study is to investigate the histopathologic findings of mucinous carcinomas including tumor border, size, associated lesion, and immunohistochemical characteristics. Method: A pathological analysis of 45 cases of pure form of mucinous carcinoma was carried out. The histologic review by light microscopy had done and followed by immunohistochemical studies. Results: The mean age of patients was 44.8 years old. The tumor borders of mucinous carcinoma were classified into pushing border in 11 cases (24.4%), partly infiltrative border in 18 cases (40.0%), and irregular infiltrative border in 16 cases (35.6%). The pure type of mucinous carcinomas had more commonly infiltrative in tumor borders and irregular shape as other malignant tumors. The mucinous carcinomas with infiltrative border were often associated with lymph node metastasis, younger ages, and association of micropapillary carcinoma in adjacent areas. The associated lesions were

micropapillary carcinomas in 5 cases (11.1%), and tubular carcinoma in 1 case (2.2%). Ductal carcinomas in situ (DCIS) were present in 28 (62.2%). In immunohistochemical study, expression of galectin-3 in tumor with DCIS was lower than in the tumor with no DCIS. Expression of synaptophysin was associated with ductal carcinoma in situ, but no difference in grade of ductal carcinoma in situ. Conclusion: The pure type of mucinous carcinomas has more commonly infiltrative border and irregular shape than well demarcated pushing border. These mucinous carcinomas are often associated with lymph node metastasis, association with micropapillary carcinoma, and young age. The mucinous carcinomas with infiltrative border may have more aggressive behavior than that to be previously known. So the mucinous tumors with infiltrative border, especially associated with micropapillary carcinoma, is needed to take notice of treatment or follow up.

Key Words: Breast, Mucinous carcinoma, Immunohistochemistry, Infiltrative border.

Introduction

Mucinous carcinoma of the breast (MCB) is a tumor containing large amounts of extracellular epithelial mucin surrounding and within tumor cells (Rosen et al, 1980; Rasmussen, 1985; Tavassoli et al, 2003). The mucinous carcinomas are characterized by a proliferation of clusters of generally small and uniform cells floating in large amounts of extracellular mucin often visible to the naked eye. They constitute about 1～7% of all breast carcinoma (Tavassoli, 1999; Tavassoli et al, 2003). It occurs in a wide range of age. The MCB are usually present as a palpable lump, pain, and nipple discharge. MCB has been classified histopathologically into pure and mixed types. Pure MCB has consisted of tumor cells with excessive extracellular mucin in the entire tumor. Mixed MCB contains areas of infiltrating ductal carcinoma (Rasmussen, 1985; Rasmussen et al, 1985; Rasmussen, 1987; Komaki et al, 1988). Because of these characteristics, mixed MCB has a more aggressive behavior, a higher rate of metastatic nodal involvement, and a decreased survival rate (Rasmussen, 1987). The mucinous carcinomas have good prognosis (Melamed et al 1961; Rosen et al, 1980). The 10-year survival rate for pure MCB was 90% to 100% (Komaki et al, 1988; Fentiman et al, 1997), whereas it was 60% in mixed MCB (Komaki et al, 1988; Paramo et al, 2002).

Pure MCB usually presents as a circumscribed lesion on a mammogram. Margins on ultrasonogram are usually well-defined lobulated lesion with expansile growth, which resemble to a benign tumor (Wilson et al, 1995; Mastuda et al, 2000). MR imaging also show

well-demarcated lobular lesion. (Kawashima et al, 2002).

Macroscopically, mucinous carcinomas show gelatinous glistering appearance and soft consistency. The tumors range from less than 1cm to over 20 cm in size, with an average of 2.8 cm. The margins appear bosselated and pushing, rather than infiltrating (Tavassoli, 1999).

Microscopically, mucinous carcinomas are characterized by proliferation of clusters of generally uniform cells with minimal amounts of eosinophilic cytoplasm, floating in abundant lakes of mucus. Delicate fibrous septa divided the mucinous lake into compartments. Epithelial component characterized by a micropapillary to solid pattern is present in 30~75%. Atypia, mitotic figures and microcalcifications are not common but occur occasionally (Tavassoli, 1999). Some mucinous carcinomas have associated with atypical hyperplasia and ductal carcinoma in situ. Some tumors have neuroendocrine differentiation (Rasmussen et al, 1986; Scopsi et al, 1994; Kato et al, 1999). Typically, mucinous carcinomas are estrogen receptor positive, while less than 70-79% are progesterone receptor positive (Komenaka et al, 2004).

Recently, surgeons have been required to remove tumor mass with more localized and restricted to lesion. In this situation, it is important to know exact characteristics for breast carcinoma including mucinous carcinomas. The authors had experienced some pure type MCB with irregular mass and infiltrative border. So the authors reviewed pure type mucinous carcinomas, and investigate the histopathologic findings of pure mucinous carcinomas, including tumor border, associated lesion and characteristics for immunohistochemistry including recently developed marker.

MaterialsandMethods

1. Materials

A. Patients

Forty-five cases of pure type mucinous carcinoma of breast were consecutively collected from Seoul National University Hospital from May 2000 to April 2005. All cases were from surgical treated women. Surgical treatments were modified radical mastectomy in 22 cases, quadrectomy with axillary lymph node dissection in 22 cases, and lumpectomy in one case. Some patients had chemotheraphy and/or radiotherapy after surgical treatment. All patients have been alive without recurrence. Tumors were classified and staged according to the sixth edition of the TNM classification of the American Joint Committee on Cancer (American Joint Committee on Cancer, 2002).

B. Antibodies

The antibodies used were estrogen receptor (ER) (1D5, DAKO, Grostrup, Denmark), progesteron receptor (PR) (PgR636, DAKO, Grostrup, Denmark), Bcl-2 clone (124, DAKO, Grostrup, Denmark), cyrokeratine (CK) 7 (OV-TL, 12/30 DAKO, Grostrup, Denmark), CK 20 (K_s 20.8, DAKO, Grostrup, Denmark), carcinoembryonic antigen (CEA) (II-7, DAKO, Grostrup, Denmark), CDX-2 (88, Biogenex, The Hague,

The Netherlands), galectin-3 (gC4, Novocastra, new castle, United Kingdum), p53 (DO-7, DAKO, Grostrup, Denmark), C-erb B2 (CB11, Novocastra, New castle, United Kingdum), Ki67 (MIB-1, DAKO, Grostrup, Denmark), neuron specific enolase (NSE) (BBS/NC/V1-H14, DAKO, Grostrup, Denmark), chromogranin (polyclonal, Zymed, South San Francisco, U.S.A.), and synaptophysin (polyclonal, DAKO, Grostrup, Denmark).

Biotinylated secondary antibody (Zymed, South San Francisco, U.S.A.) as secondary antibody, streptovidin-HRP (Zymed, South San Francisco, U.S.A.) as enzyme conjugate, and diaminobenzidine (DAB) chromogen (Zymed, South San Francisco, U.S.A.) used.

2. Method

A. Histopathologic evaluation

The resected surgical specimens were fixed in 10% formalin and four to seven representative sections of the primary tumor were submitted for microscopic examination. The sections were fixed in formalin, embedded in paraffin wax, and stained with hematoxilin and eosin.

The tumors in all 45 cases were received by light microscopic examination. The following features were recorded: tumor border, tumor size, large/small dimension ratio, presence of ductal carcinoma in situ and their histologic subtype and grade by Van Nuey's classification, other associated lesions, and lymph node metastasis. Associated secondary carcinoma was defined as a definitively separated carcinoma with presence of normal breast tissue of more than 1 cm width

between the mucinous carcinoma and associated lesion.

B. Immunohistochemistry and interpretation

Immunohistochemical stains were preformed in 43 cases.

Four micron sections were deparaffinized, rehydrated in graded alcohols, and processed using avidin-biotin immunoperoxidase methodology. Briefly, antigen was retrieved by exposure in a microwave oven for 15 min in 10 mM citrate buffer pH 6.0. Endogenous peroxidase activity was blocked with a 3% H_2O_2 solution, and the slides were incubated in 10% normal goat serum for 30 minutes to prevent nonspecific staining. They were then incubated for 1 hour at room temperature in appropriately diluted primary antibody. Thereafter the sections were incubated with biotinylated secondary antibodies, followed by avidin-biotin peroxidase complexes for 30 minutes. DAB was used as chromogen, and Mayer's hematoxylin as counterstain. As a negative control, Tris-buffered saline was substituted for the primary antibody.

Expressions of ER, PR, p53, and Ki67 were in nuclei. Expressions of Bcl-2, CK7, CK20, CEA, CDX-2, galectin-3, NSE, chromogranin and synaptophysin were in cytoplasm. Expression of C-erb B2 was in cell membrane.

Cut-off limits for positive staining was chosen ER ≧10%, PR ≧10%, Bcl-2 ≧10%, and p53 ≧1% irrespective of the intensity of the staining. C-erbB2 immunostaining was considered negative in no or weak (1+) membrane staining, and positive in moderate (2+) or strong (3+) membrane staining. MIB labeling index, Ki67 staining, was classified

into two groups: <2% and ≧2%. The staining was performed in an automatic staining machine (Techmate^{TM} 500 Plus, DAKO inc, Grostrup, Denmark)

C. Statistical analysis

Statistical analysis was performed with SPSS software (version 11.5, SPSS Inc. Chicago, IL). Chi-square or Fisher's exact tests were used when comparing frequencies between groups. All numerical data were expressed as means±SD, and differences between means of groups were compared by independent samples T test. Probability values less than 0.05 or 0.1 were considered statistically significant.

Results

1. General features

The patients mainly present with palpable lump in breast, and 5.7 months in mean duration. The mean age at presentation was ranged from 29 to 89 years old (mean: 44.8 years). Microcalcifications at tumor mass were present in 15 out of 45 cases (34.1%). Some tumors had multiple masses with pure type mucinous carcinomas and other type carcinoma or pure type mucinous carcinoma.

2. Histopathologic analysis

The average size of the tumors was 2.2 x 1.7 cm, and ranged in size from 0.4 cm to 15 cm. Most of pure type mucinous carcinomas were stage I or II (Table 1). The tumor masses were T1 in 23 cases, T2 in 19 cases, and T3 in 3 cases. The tumor mass had abundant mucin pool with some clusters of floating cell nest (Figure 1). The tumor borders of mucinous carcinoma were classified into 3 types, as pushing border, partly infiltrative border, and infiltrative border. The pushing border type was defined as distinctly smooth border and completely well-demarcation with no infiltration to adjacent surrounding parenchyme (Figure 2). The pushing border type was in 11 cases (24.4%) (Table 2). The partly infiltrative border was defined as focal to partial irregular border, even though mainly well demarcated. Some nests of tumor cells were present in adjacent surrounding parenchyme

of tumor mass with infiltration (Figure 3). The partly infiltrative border type was in 18 cases (40.0%). The infiltrative border was defined as irregular border with infiltration to adjacent surrounding parenchyme by multiple tumor cell nest (Figure 4). The irregular border type was in 16 cases (35.6%). The averages of tumor sizes were 3.30 x 2.10cm in tumor with pushing border, 2.25 x 1.74 cm in partly infiltrative border, and 2.30 x 1.70 cm in infiltrative border. There was no correlation between tumor border type and tumor size or stage. But, in standardized cases, which were excluded of largest or smallest, the tumor sizes were 1.80 x 1.61 cm in pushing border, 1.89 x 1.50 cm in partly infiltrative border, and 2.40 x 1.75 cm in infiltrative border. The tumor border had a tendency of becoming irregular with the increase of tumor size. Large/small dimension ratio were 1.57 in pushing border, 1.29 in partly infiltrative border, and 1.35 in infiltrative border in all cases. The tumor had a tendency of more larger and more irregular shaped mass becoming the tumor border more infiltrative.

3. Lymph node metastasis

The metastasis to axillary lymph nodes were present in 4 out of all 45 cases (8.9%) (Table 3). No metastasis to other organ was present. The one was found in group of tumors with partly infiltrative border and the other three cases were present in groups of tumors with infiltrative borders. The tumor group with pushing border had no case with metastasis to lymph nodes. The mean size of the tumors with metastatic lymph node was 4.0 x 2.9 cm. The age of patients belonged

to this group were 29~66 years old. Only one case with 66 years old. The other three cases are about 30 years old. According to TNM systems, two cases account for pN1, one case for pN2, and one case for pN3.

3. Associated lesions

Ductal carcinomas in situ (Figure 5) were associated in 28 (62.2%) out of total 45 mucinous carcinomas (Table 4). They were accompanied in 6 cases (54.5%) of tumor with pushing border, 8 cases (44.4%) of the partly infiltrative border, and 14 cases (87.5%) of the infiltrative border. The tumor with more irregular tumor border had a tendency to have ductal carcinoma in situ around the tumor. But the tumor border patterns were not correlated with Van Nuey's grade or histologic pattern. Out of 28 ductal carcinoma in situ, 17 cases (60.7%) showed micropapillary and papillary pattern, which were more frequent in tumor with infiltrative border. Five cases (17.8%) showed cribriform pattern.

The other associated lesions were micropapillary carcinoma (figure 6) in 5 cases (11.1%), and tubular carcinoma (figure 7) in 1 case (2.3%) (Table 5). Three out of 5 cases of micropapillary carcinomas belonged to tumor with partly infiltrative border, and two to tumor with infiltrative border. Three out of 5 cases with second carcinoma of micropapillary type were associated with lymph node metastasis. In three cases with lymph node metastasis, tumor border were infiltrative in two cases and partly infiltrative in one case. The pure type mucinous carcinoma with tubular carcinoma had tumor border with pushing type

and no lymph node metastasis.

4. Immunohistochemical result

The result of immunohistochemical study of pure type mucinous carcinomas were summarized (Table 6).

ER and PR expression were no different in each groups according to tumor border. Immunoreactivity for Bcl-2 showed a tendency of decrease with more irregular tumor border, which expressed in 11 cases (100%) out of 11 tumor with pushing border, 14 (82.4%) out of 17 cases with partly infiltrative border, and 12 (80.0%) out of 15 cases of tumor with infiltrative border. In C-erb B2 expression, 34 cases (79.1%) were negative, and 9 (20.9%) in positivity (Figure 10). In p53 expression, 37 cases (86.0%) were positive. Twenty eight (65.1%) out of 43 cases of pure type mucinous carcinomas showed reactivity for galectin-3.

In tumors with DCIS, expression of galectin-3 was positive in 14 (51.9%), but tumor with no DCIS showed positivity in 14 cases (87.5%) (Figure 11) (Table 7). Immunoreactivity for galectin-3 did not show any correlation with expression of p53.

In immunohistochemical study for neuroendocrine differentiation, pure type mucinous carcinomas showed reactivity in 23 (53.5%) out of 43 cases for NSE expression, reactivity in 10 (23.3%) for synaptophysin (Figure 12), and reactivity in 27 (62.8%) for chromogranin (Table 6). In counting of number of positive neuroendocrine markers, 33 cases (76.7%) of pure type mucinous carcinoma had one or two positivity for three neuroendocrine markers. One cases (9.1%) of tumor with pushing

border and 4 cases (26.7%) out of 15 tumor with infiltrative border did not show any neuroendocrine marker (Table 8).

In immunoreactivity for synaptophysin, tumor with DCIS was positive in 9 cases (33.3%), however tumor with no DCIS showed positivity in only one case (6.3%). In immunoreactivity for chromogranin, tumor with DCIS was positive in 15 cases (55.6%), but tumor with no DCIS showed positivity in 12 cases (75.0%). In discrimination according to grade of DCIS, only Ki67 expression showed significancy, which showed positivity in 5 cases (31.3%) in low grade, in 2 cases (100%) in intermediate grade, and in 7 cases (77.8%) in high grade (Table 9).

Discussion

The pure type mucinous carcinomas are known to be well-demarcated tumor (Rasmussen, 1985). The margins of this tumor have been known to appear bosselated and pushing, rather than infiltrating (Tavassoli, 1999). But in the present study, the pure type mucinous carcinomas showed more commonly irregular tumor border than well-demarcated pushing border. Even though well-demarcated pushing border at first sight, many of the pure type mucinous carcinomas had infiltrative border to surrounding soft tissue. The tumors with well-demarcated pushing type border were somewhat round shaped lesion. But the tumor with infiltrative border were more or less oval or irregular shaped lesion. The tumor size had no correlation with type of tumor border.

Pure type mucinous carcinomas are slowly growing tumors, and has favorable prognosis (Rasmussen, 1985; Clayton, 1986; Rasmussen, 1987; Komenaka et al, 2004). The majority of pure type mucinous carcinomas presented at stage I or II (Komenaka et al, 2004). In present study, it showed similar results. It is suggested that tumor size itself is not a significant prognostic factor, perhaps because the large volume of mucin may lead to overestimation of tumor burden (Komenaka et al, 2004). The number of involved axillary lymph nodes is the most significant predictor of death from disease in mucinous carcinoma (Clayton, 1986; Fentiman et al, 1997; Komenaka et al, 2004).

In present study, two cases with pushing border had huge mass measuring 15.5 x 5.0 cm and 5.3 x 3.5 cm each other. But they were

confined in original place for a long duration and no lymph node metastasis in spite of huge tumor size. It may be the distinctive characteristic features of the tumor with pushing border. In present study, all three cases, one tumor with pushing border and two tumors with infiltrative border, were present in stage III. The one tumor with pushing border was stage III due to its large size (T3). On the other hand, two tumors with infiltrative border was stage III due to lymph node metastasis. The tumor with infiltrative border had a tendency of lymph node metastasis relatively early and at relatively small size than tumor with pushing border in tumor progression. The tumors with infiltrative border were more ovoid or irregular shaped lesion, and had a tendency of relatively more frequent metastasis than tumors with pushing border.

Tumor size, favorable histology (mucinous, papillary, and tubular carcinomas), lower histologic grade, and increasing age were associated significantly with a lower frequency of axillary lymph node metastases in breast carcinoma (Komaki et al, 1988; Diab et al, 1999; Meibenco et al, 1999; Paramo et al, 2002). In pure type mucinous carcinoma, the incidence of axillary metastases is variably reported in ranged 2% to 14% (Clayton, 1986; Fentiman et al, 1997; Avisar et al, 1998; Paramo et al, 2002). In present study, the incidence of lymph node metastasis is 8.8%. In present study, lymph node metastasis in pure type mucinous carcinomas was associated with infiltrative tumor border, younger age, and coexistence of micropapillary carcinoma.

Mucinous carcinomas are often associated with ductal carcinoma in situ in present study. In the previous study, ductal carcinoma in situ

was present in 15~37% of pure type mucinous carcinomas (Maluf et al, 1995; Chinayama et al, 1996), and has a micropapillary pattern in 30~75% (Tavassoli, 1999). In present study, ductal carcinoma in situ coexisted in 28 cases (63.4%), and ductal carcinoma in situ was more frequently found in tumors with infiltrative border. The pure type mucinous carcinomas with irregular border of partly infiltrative or infiltrative border had a tendency to be associated with ductal carcinoma in situ more frequently.

The other coexisted lesions with pure type mucinous carcinoma in this study were micropapillary carcinomas and a tubular carcinoma. Micropapillary carcinomas were most common coexisted lesion of relatively high prevalence of 11.4% (5 cases) out of all pure type mucinous carcinomas. There is no report about prevalence of mucinous carcinoma coexisted with micropapillary carcinoma. These micropapillary carcinomas were located outside of the mucinous carcinomas, and characteristically found in the tumors with more irregular tumor border and lymph node metastasis. Usually, micropapillary carcinoma is associated with high incidence of metastasis to lymph nodes and poor clinical outcome (Luna-More et al, 1994; Peterakos et al, 1999). Invasive ductal carcinoma with micropapillary carcinoma component is related to greater tumor size, more frequent nodal metastasis, and higher stage than usual invasive ductal carcinoma with no micropapillary component (Kim et al, 2005). In the present study, mucinous carcinomas coexisted with papillary carcinoma had higher incidence of lymph node metastasis, found in 3 out of 4 cases (75%) of pure type mucinous carcinomas. Even limited by small number of data, coexistence of mucinous

carcinoma with micropapillary carcinoma may be related to more poor prognosis.

Mucinous carcinomas are known to be ER positive, while less than 70% are PR positive (Tavassoi, 1999; Komenaka et al 2004). Immunoreactivities for ER and PR were similar to previous study, and were not different in each groups in this study. Immunoreactivity for Bcl-2 showed a tendency of decrease with becoming the tumor border more irregular, but not with statistical significance. Expression of C-erb B2 increased with coexistence of ductal carcinoma in situ and their higher Van Nuey's grade, but also with no statistical significance. Positive correlation between p53 and galectin-3 expression was noted in ductal carcinoma in the previous study for breast carcinomas (Shekhar et al, 2004). However, in present study, there was no correlation between galectin-3 expression and p53 expression in tumor cells. Some demonstrate that galectin-3 expression correlates with tumor progression including the ability of cancer cells to metastasize and with decreased patient survival (Ochieng et al, 1998; Miyazaki et al, 2002). In present study, galectin-3 expression was present in 28 cases (63.6%). Galectin-3 expression decreased significantly in pure type mucinous carcinomas with ductal carcinoma in situ. This result is similar to previous other studies, which galectin-3 expression decreased in low grade of ductal carcinoma in situ and increased with progression of infiltrating duct carcinoma (Idikio, 1998; Ochieng et al, 1998; Shekhar et al, 2004).

It was reported that some mucinous carcinomas of breast have neuroendocrine differentiation (Rasmussen et al, 1986; Scopsi et al, 1994; Kato et al, 1999). It is reported that argyrophilia implies a worse

prognosis in a series of pure and mixed (partial) mucinous carcinomas (Cubilla et al, 1984). However one recent study showed that NSE expression is associated with good prognosis (Markretsov et al, 2003). Another study showed that neuroendocrine differentiation in pure mucinous carcinoma is associated with lower nuclear grade and lower axillary lymph node metastasis (Tse et al, 2004). In present study, expression of neuroendocrine markers had no correlation with type of tumor border. Although there was no statistical significance, tumors positive for all three nueroendocrine markers were relatively common in tumors with pushing border. However tumor with no reactivity for any neuroendocrine were relatively common in tumor with infiltrative border. In other breast cancer study, synaptophysin expression was correlated with higher tumor grade, and NSE expression was correlated with good prognosis (Markretsov et al, 2003). In present study, only expression of synaptophysin was associated with coexistence of ductal carcinoma in situ, but with no correlation with grade of ductal carcinoma in situ.

Conclusion

The pure type of mucinous carcinomas have more commonly infiltrative borders and irregular shape as other malignant tumors. The mucinous carcinomas with infiltrative border are often associated with lymph node metastasis, younger ages, and coexistence of micropapillary carcinoma. Even limited by small number of data, mucinous carcinomas coexisted with micropapillary carcinoma may be related with more poor prognosis.

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국문 초록

순수형 유방점액암종의 조직학적 검토와 면역조직학적 분석

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배경 : 순수형 유방점액암종은 종양의 경계가 좋고 비교적 덜 공격적인 생물학적 행태를 보이며 예후가 좋은 것으로 알려져 있다. 본 연구의 목적은 종양의 경계, 크기, 다른 동반된 악성 병변 그리고 면역조직학적 검사 등을 포함한 유방점액암종의 여러 특성을 조직병리학적 탐구하고 밝히는데 있다. 방법: 순수 유방점액암종 45 증례를 모아서 병리학적 검토 및 분석을 시행하였다. 환자는 모두 2000년에서 2005년 사이에 외과적 치료를 받았다. 광학 현미경적 검사를 통해 조직학적 검토를 하고, 면역조직화학적 검사를 시행하였다. 결과: 환자의 평균 연령은 44.8세이다. 종양의 경계는 미는 유형의 경계가 11례 (24.4%)였고, 부분 침습형 경계가 18례 (40.0%), 그리고 불규칙적 침습형 경계가 16례 (35.6%)였다. 종양의 경계는 알려진 바와는 달리, 미는 유형보다는 오히려 침습형 경계가 보다 흔하였다. 관내 상피내암이 모두 45례의 점액양 암종 중에서 28례 (62.2%)에서 동반되었다. 관내 상피암이 동반은 침습형 경계를 가지는 암종에서 보다 흔히 동반되어 나타났다. 그 외 동반되어 나타는 다른 병변으로 5례(11.1%)의 미세유두상암종이 있었고, 1례(2.2%)의 관암종이 있었다. 미세유두상 암종은 보다 침습형의 경계를 가지는 경우에 동반되었다. 침습형 경계를 가진 유방점액암종은

림프절 전이가 흔히 있었고, 젊은 나이, 미세유두상암종이 동반되었다. 관내 암종은 미는 유형의 경계를 가지는 경우에서 동반되었다. 보다 경계가 불규칙적인 경계를 가지는 암종은 관내상피암이 잘 동반되는 경향을 보였다. 점액양 암종에 대한 면역조직화학적 검사에서 galectin-3는 관내상피암종이 동반된 경우 관내상피암종이 동반되 경우에 비해 발현이 감소하였다. synaptophysin은 관내상피암종이 동반된 경우 발현이 동반된지 않은 경우보다 증가하였다. 결론: 순수형 유형점액암종은 경계가 좋은 미는 유형보다, 경계와 모양이 불규칙적인 침습형 경계가 보다 흔하다. 이는 이전에 알려진 것보다 공격적인 형태이다. 따라서 외과적 수술시에 종양의 경계 유형에 주의하여야하고, 침윤성 경계를 가지는 유방점액암종의 치료 및 추적관찰에 유의할 필요가 있다.

Table 1. The tumor stage in pure type mucinous carcinomas of breast according to TNM system of AJCC.

border / stage	pushing		partly infiltrative		infiltrative		total	
	No.	%	No.	%	No.	%	No.	%
I	5	45.5	12	66.7	6	37.5	23	51.1
IIa	4	36.4	4	22.2	6	37.5	14	31.1
IIb	1	9.0	2	11.1	2	12.5	5	11.1
IIIa	1	9.0	0	0.0	1	6.3	2	4.4
IIIb	0	0.0	0	0.0	0	0.0	0	0.0
IIIc	0	0.0	0	0.0	1	6.3	1	2.2
Total	11	100	18	100	16	100	45	100

Table 2. Tumor border of 45 patients with pure type mucinous carcinomas of breast.

Border type	Pushing		partly infiltrative		infiltrative		total	
	No.	%	No.	%	No.	%	No.	%
size								
<2cm	5	45.5	12	66.7	6	37.5	17	37.8
2~5cm	4	36.4	5	27.8	10	62.5	15	33.3
>5cm	2	18.2	1	5.6	0	0.0	13	28.9
mean size								
all cases	3.30x2.09cm		2.25x1.70cm		2.30x1.70cm		2.50x1.81cm	
standardized cases*	1.80x1.61cm		1.89x1.50cm		2.40x1.75cm		2.00x1.63cm	
Large/small diameter ratio								
all cases	1.57		1.29		1.35		1.29	
standardized cases	1.12		1.26		1.37		1.23	
case number	11		18		16		45	
% to total	24.4		40.0		35.6		100.0	

* standardized cases: exclude largest and smallest at all cases.

Table 3. Incidence and characteristics of four cases of pure type mucinous carcinoma with lymph node metastasis.(N=4)

		No	%
tumor border	pushing	0	0
	partly infiltrative	1	25
	infiltrative	3	75
No. of involved lymph node	0-3	2	50
	4-9	1	25
	>10	1	25
tumor size	<2cm	0	
	2~5cm	4	100
	>5cm	0	
associated lesion	DCIS	4	100
	micropapillary carcinoma	3	75

DCIS: ductal carcinoma in situ

Table 4. Ductal carcinoma in situ and Van Nuey's histologic grade in pure type mucinous carcinomas with each tumor border.

type of tumor border / grade	pushing		partly infiltrative		infiltrative		total	
	No.	%	No.	%	No.	%	No.	%
low	4	66.7	4	50.0	9	64.3	17	60.7
intermediate	0	0	1	12.5	1	7.1	2	7.1
high	2	33.3	3	37.5	4	28.6	9	32.1
cases of each type * No.	6		8		14		28	
cases of each type * %	54.5		44.4		87.5		62.2	

* $P<0.05$

Table 5. Histologic type of secondary associated invasive carcinoma in cases of pure type mucinous carcinomas.

associated lesion		pushing (n=11)	partly infiltrative (n=18)	infiltrative (n=16)	total (n=45)
micropapillary carcinoma		0	3	2	5
tubular carcinoma		1	0	0	1
total	No.	1	3	2	6
	%	9.0	16.7	12.5	13.3

Table 6. Immunohistochemical expression in pure type mucinous carcinoma with each border type.

	pushing		partly infiltrative		infiltrative		total		p value
	No.	%	No.	%	No.	%	No.	%	
ER	11	100	16	94.1	14	93.3	42	95.5	NS
PR	8	72.7	14	82.4	11	73.3	33	76.7	NS
Bcl 2	11	100	14	82.4	12	80.0	37	86.0	NS
C-erb B2	1	9.1	4	23.5	4	26.7	9	20.9	NS
p53	10	90.9	13	76.5	14	93.3	37	86.0	NS
Ki67*	5	45.5	11	64.7	7	46.7	23	53.5	NS
CK 7	8	72.7	14	82.4	12	80.0	34	79.1	NS
CK 20	0	0	1	5.9	0	0	1	2.3	NS
CEA	0	0	4	23.5	4	26.7	8	18.6	NS*
CDX2	0	0	0	0	0	0	0	0	
galectin-3	7	63.6	13	76.5	8	53.3	28	65.1	NS
NSE	9	81.8	7	41.2	7	46.7	23	53.5	0.088
synaptophysin	3	27.3	3	17.6	4	26.7	10	23.3	NS
chromogranin	7	63.6	14	82.4	6	40.0	27	62.8	0.047
total	11	100	17	100	15	100	43	100	

ER: estrogen receptor, PR: progesteron receptor, CK: cytokeratin, CEA: carcinoembryonic antigen, NSE: neuron specific enolase.

* Ki67≧2%

Table 7. Immunohistochemical expression in pure type mucinous carcinoma with ductal carcinoma in situ.

DCIS / Antibodies	absent		present		total		p value
	No.	%	No.	%	No.	%	
ER	15	100.0	25	92.6	41	95.3	NS
PR	14	87.5	19	70.4	33	76.7	NS
Bcl-2	13	81.3	24	88.9	37	86.0	NS
C-erb B2	1	6.3	8	29.6	9	20.9	0.069
p53	13	81.3	24	88.9	37	86.0	NS
Ki67*	9	56.3	14	51.9	23	53.5	NS
CK 7	15	93.8	19	70.4	34	79.1	0.069
CK 20	0	0	1	3.7	1	2.3	NS
CEA	2	12.5	6	22.2	8	18.6	NS
CDX2	0	0	0	0	0	0	
galectin-3	14	87.5	14	51.9	28	65.1	0.018
NSE	8	50.0	15	55.6	23	53.5	NS
synaptophysin	1	6.3	9	33.3	10	23.3	0.042
chromogranin	12	75.0	15	55.6	27	62.8	NS
total	16	100	27	100	43	100	

DCIS: ductal carcinoma in situ, ER: estrogen receptor, PR: progesteron receptor, CK: cytokeratin, CEA: carcinoembryonic antigen, NSE: neuron specific enolase,

* Ki67≧2%

Table 8. Number of positive neuroendocrine marker in pure type mucinous carcinoma with each border type.

Count of positive expression	pushing		partial infiltrative		infiltrative		total	
	No.	%	No.	%	No.	%	No.	%
0/3	1	9.1	0	0	4	26.7	5	11.6
1/3	4	36.4	11	64.7	6	40.0	21	48.8
2/3	3	27.3	5	29.4	4	26.7	12	27.9
3/3	3	27.3	1	5.9	1	6.7	5	11.6
total	11	100	17	100	15	100	43	100

p value: 0.078

Table 9. Immunohistochemistry in tumor with Van Nuey's grade of ductal carcinoma in situ associated.

	nuclear grade						total tumor with DCIS		p value
	low		intermediate		high				
	No.	%	No.	%	No.	%	No.	%	
ER	15	93.8	2	100	8	88.9	25	92.6	NS
PR	12	75.0	2	100	5	55.6	19	70.4	NS
Bcl 2	15	93.8	2	100	7	77.8	24	88.9	NS
C-erb B2	4	25.0	0	0	4	44.4	8	29.6	NS
p53	14	87.5	2	100	8	88.9	24	88.9	NS
Ki67*	5	31.3	2	100	7	77.8	14	51.9	0.030
galectin 3	8	50.0	1	50	5	55.6	14	51.9	NS
NSE	10	62.5	1	50.0	4	44.4	15	55.6	NS
Synaptophysin	3	18.8	1	50	5	55.6	9	33.3	NS
Chromogranin	9	56.3	1	50	5	55.6	15	55.6	NS
total	16	100	2	100	9	100	27	100	

DCIS: ductal carcinoma in situ, ER: estrogen receptor, PR: progesteron receptor, NSE: neuron specific enolase.
* Ki67≧2%

김동출 박사학위논문 사진부도(1)

Figure 1. Microscopically mucinous carcinoma showed nests of tumor cells in extracellular mucin pool.

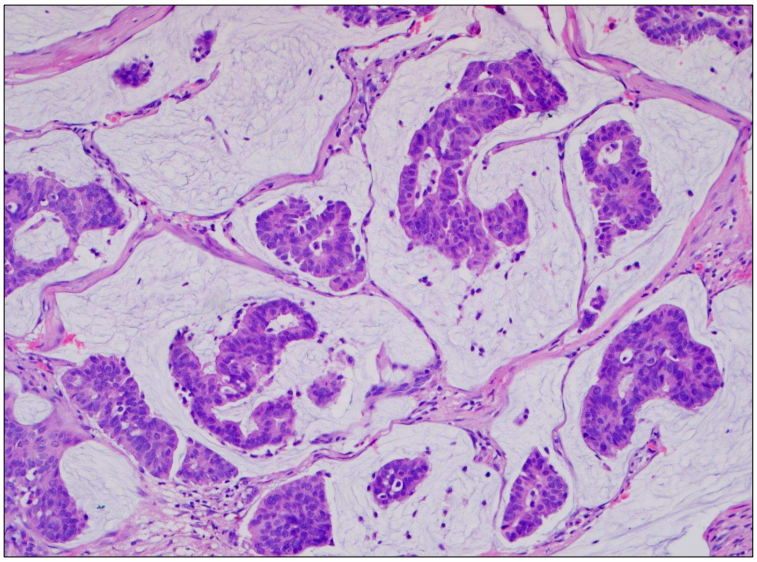
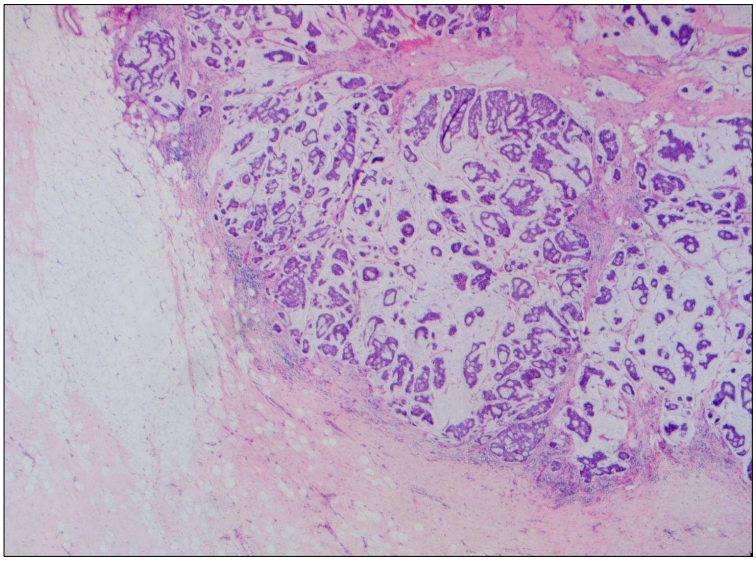


Figure 2. Pushing type mucinous carcinoma. The mucinous carcinoma had smooth well-demarcated border.



김동출 박사학위논문 사진부도(2)

Figure 3. The mucinous carcinoma with partly infiltrative border. Some tumor nests and mucin pool were present in surrounding soft tissue.

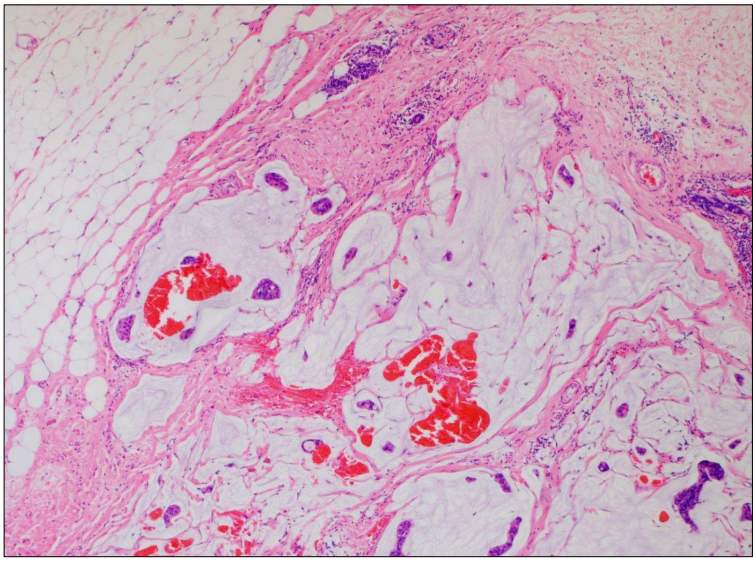
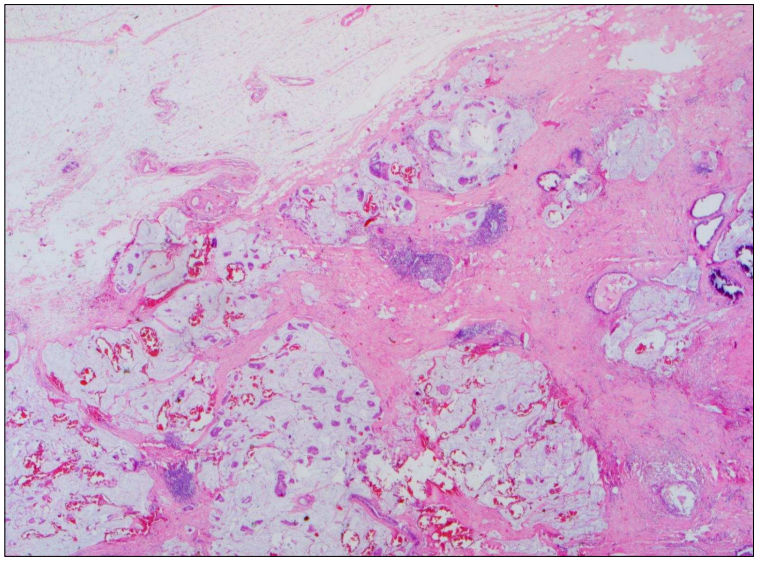


Figure 4. The mucinous carcinoma with infiltrative border. The mucinous carcinoma had irregular ill-defined lesion.



김동출 박사학위논문 사진부도(3)

Figure 5. Ductal carcinoma in situ with papillary pattern was present in pure type mucinous carcinoma.

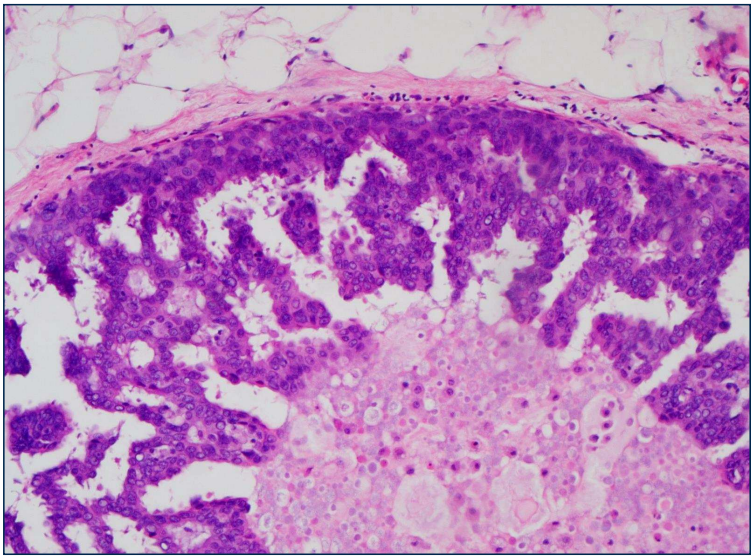
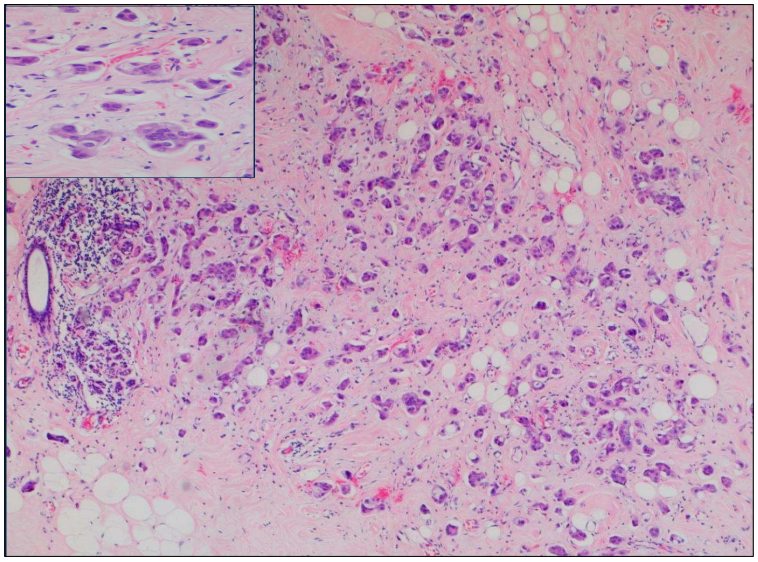


Figure 6. Micropapillary carcinoma was associated in outside of pure type mucinous carcinomas.



김동출 박사학위논문 사진부도(4)

Figure 7. Tubular carcinoma was associated in outside of pure type mucinous carcinoma.

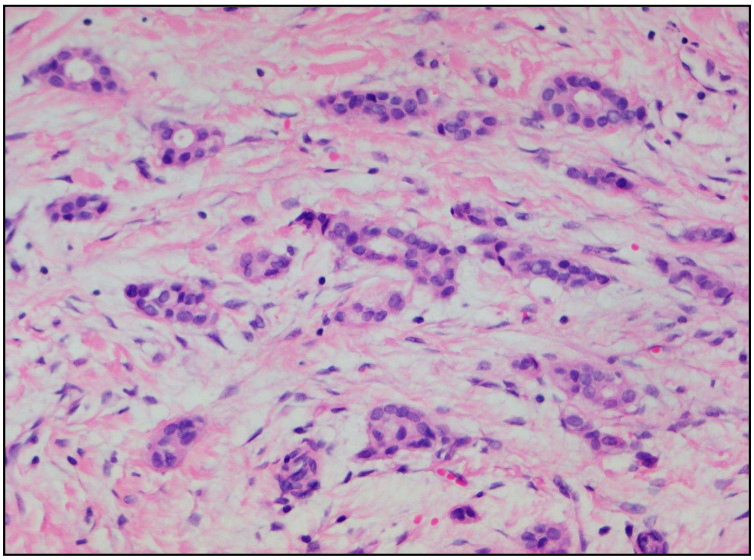


Figure 8. Immunohistochemical staining of pure type mucinous carcinoma for estrogen receptor showed strong nuclear reactivity of tumor cells.

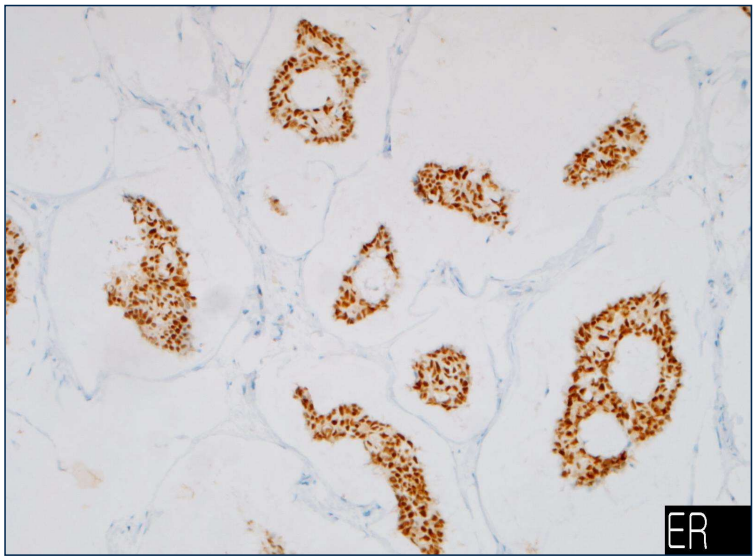


Figure 9. Immunohistochemical staining of pure type mucinous carcinoma for Bcl-2 showed reactivity in cytoplasm.

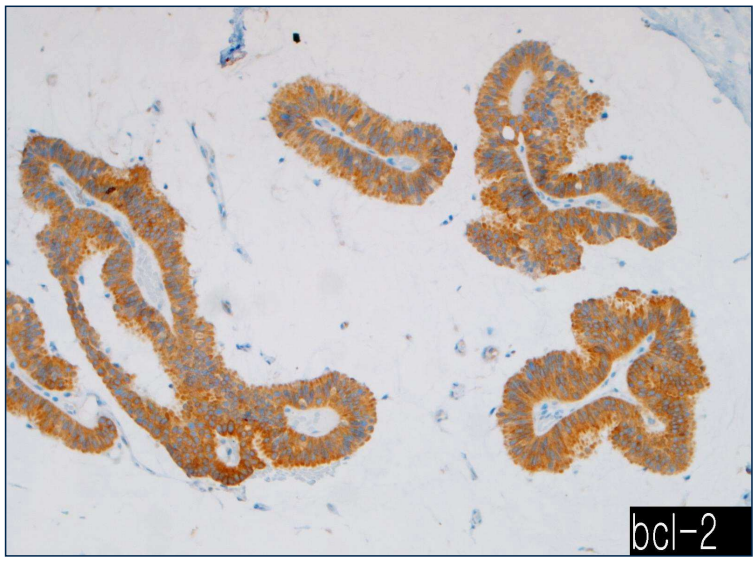
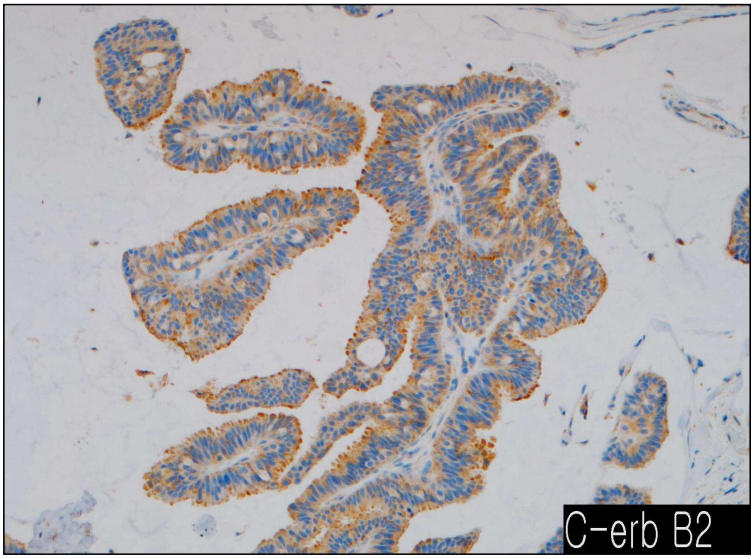


Figure 10. Immunohistochemical staining of pure type mucinous carcinoma for C-erb B2 showed positive reactivity in cell membrane.



김동출 박사학위논문 사진부도(6)

Figure 11. Immunohistochemical staining of pure type mucinous carcinoma for galectin-3 showed positivity in cytoplasm.

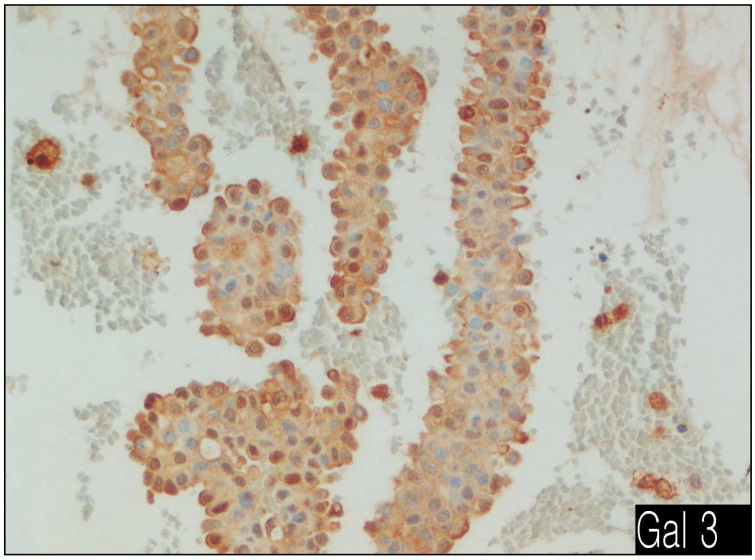


Figure 12. Immunohistochemical staining of pure type mucinous carcinomas for synaptophysin showed positive reactivity in cytoplasm.