

Primary Carcinoma of the Gallbladder

—An Analysis of 34 Cholecystectomy Cases with Special Reference to Metaplastic Changes—

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INTRODUCTION

Primary gallbladder carcinoma is generally assumed as uncommon but dismal malignancy¹⁾. Only sporadic studies about pathologic features of the gallbladder carcinoma have drawn pathologists' attention especially in association with cholelithiasis^{2,3)}. Currently, we have focused much on the role of metaplastic changes in diseased gallbladders including cholecystitis with or without cholelithiasis⁴⁾, and raised its implication in the development of benign or malignant neoplasm⁵⁾.

The authors reviewed 34 cholecystectomy cases with primary gallbladder carcinoma, and their histologic findings were analyzed with reference to the association of metaplastic changes both in tumor and adjacent nonneoplastic mucosal epithelium.

MATERIALS AND METHODS

A total of 34 cholecystectomy cases diagnosed as primary gallbladder carcinoma during a period of 1980 to 1986 were retrospectively collected from the pathology files of Seoul National University Hospital for review. Both tumorous and adjacent nonneoplastic mucosal portions were available in most of cases.

Paraffin blocks from each case were serially recut

for additional hematoxylin-eosin staining, and al-cian blue-PAS (pH 2.5) staining was applied to every case. In addition, Churkian Schenk stain was used to localize intratumoral argyrophil granules in 17 cases. Gross findings were reviewed with photography and pathologic reports. The full clinical history was available in 27 patients and reviewed with particular attention to association of cholelithiasis. Follow-up period after operation was from 1 to 20 months in 18 cases.

RESULTS

The age and sex distribution of 34 cases are shown in Fig. 1. As expected, there was a slight predominance of females (F : M=20 : 14). The age at the time of diagnosis varied from 28 to 73 years (average 58.1 years). Three cases expired 1 to 3 months after operation and another three had clinical evidence of the disease.

Histologic types of these 34 cases are summarized in Table 1. Thirty out of 34 cases were adenocarcinoma, and the remaining 4 cases were unusual types such as signet ring cell carcinoma, mucoepidermoid carcinoma, pleomorphic spindle cell carcinoma and carcinosarcoma.

Microscopically 30 cases of adenocarcinoma were divided into two histologic subtypes, non-intestinal (19 cases, 63%) and intestinal types (11 cases, 37%). The histologic pattern of the former was composed of dispersed glandular and tubular structures of variable size in background of dense fibrosis. The

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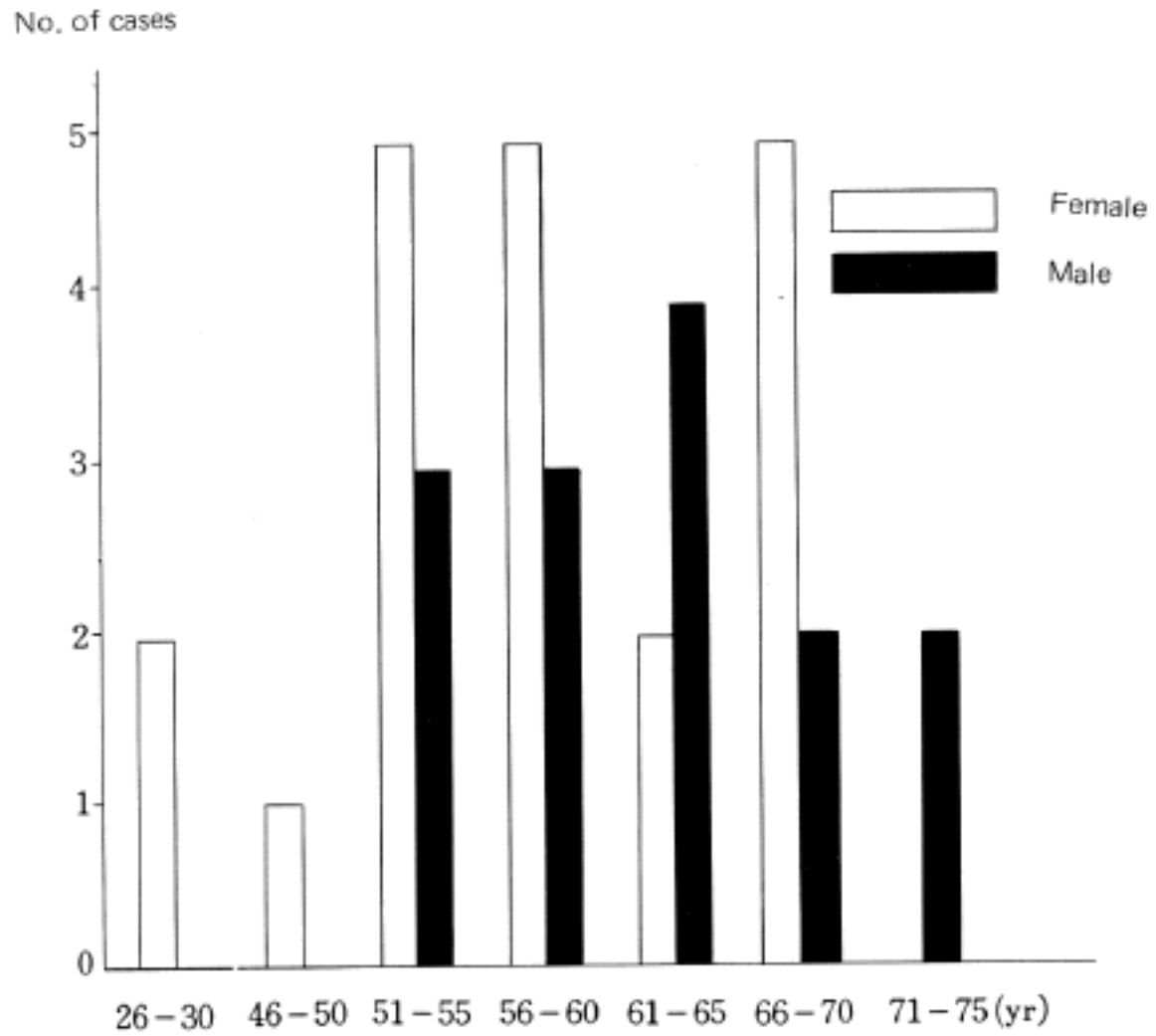


Fig. 1. Age distribution of 34 primary gallbladder carcinomas.

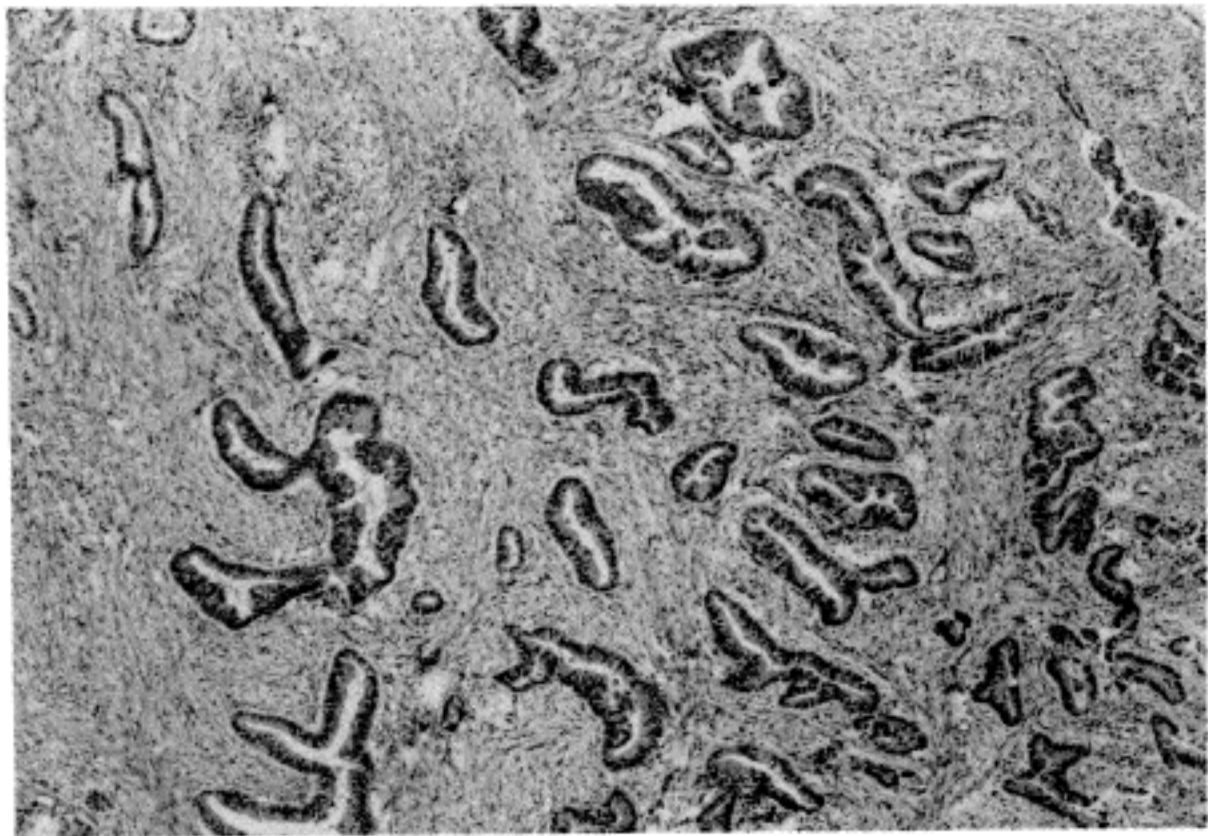


Fig. 2. Non-intestinal type adenocarcinoma. It is composed of branching tubules and glands of variable size with dense fibrosis. (H&E, $\times 40$)

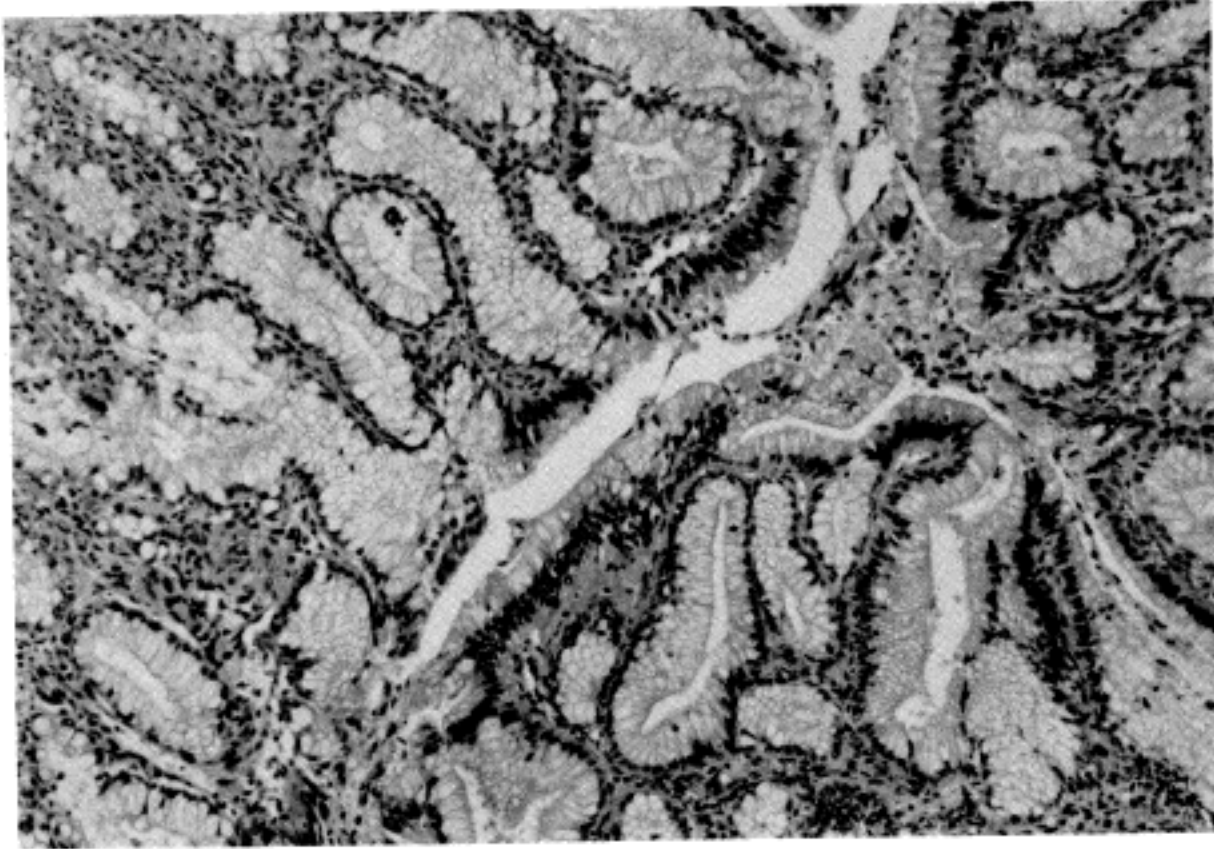


Fig. 3. Intestinal type adenocarcinoma. It resembles colonic mucosa, being composed of goblet cells and absorptive columnar cells. (H&E, $\times 200$)

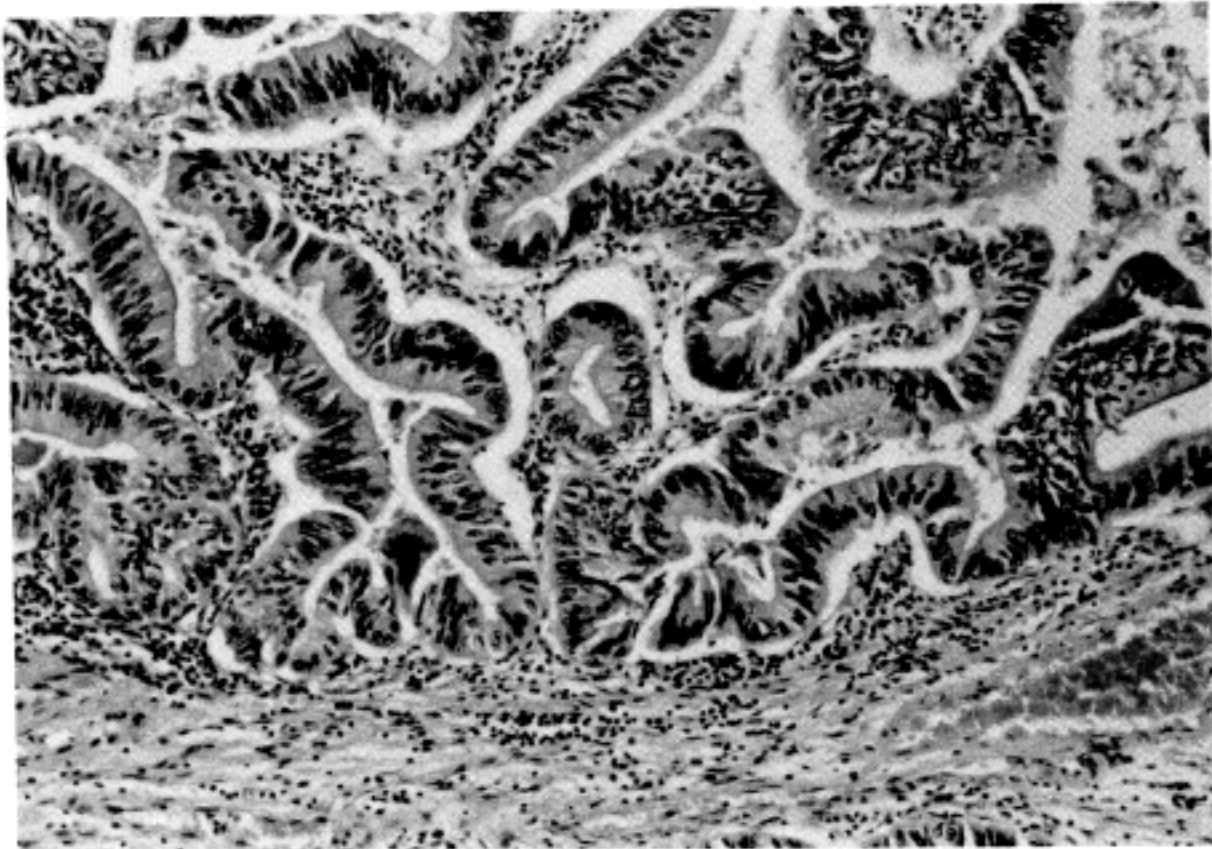


Fig. 4. Papillary growth in intestinal type adenocarcinoma. Well formed brush border along the luminal surface is one of characteristic features. (H&E, $\times 200$)

glandular structures were lined by cuboidal or columnar epithelium which were stratified in some areas and contained little amount of intracytoplas-

mic mucin (Fig. 2). On the other hand, the latter showed the following characteristics; 1) predominance of goblet cells and mucin secreting columnar

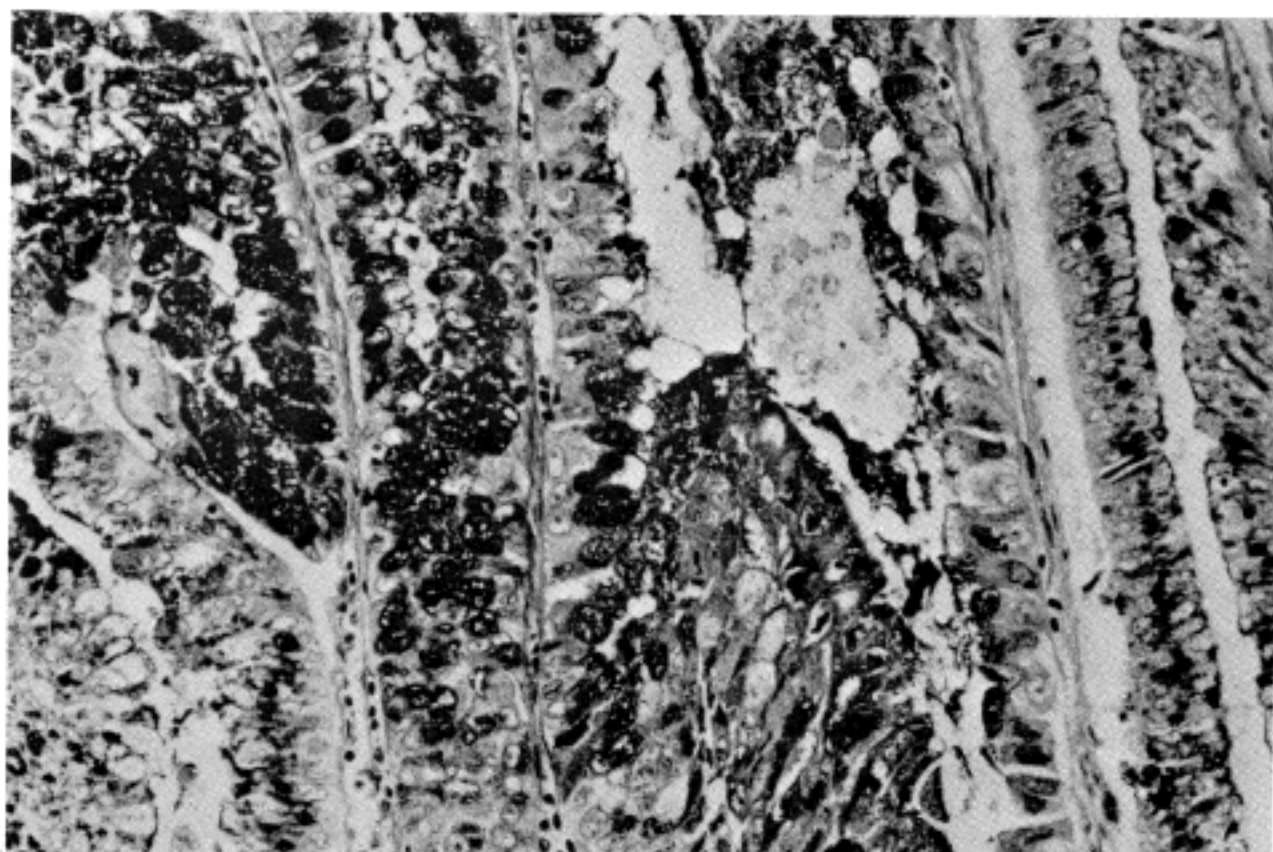


Fig. 5. Intracytoplasmic mucin in intestinal type adenocarcinoma. Note the dark stained Alcian blue positive mucin in most of tumor cells. (Alcian blue-PAS at pH 2.5, $\times 400$)

cells (Fig. 3), 2) well developed brush border of the tumor glands along the apical surface (Fig. 4), 3) abundant acid mucin in tumor glands and stroma, 4) presence of antral type glands in lower portion of neoplastic glands. On hematoxylin-eosin stain, papillary or complexed glandular structures exhibited varying numbers of goblet cells admixed between tall columnar cells which were positive on alcian blue staining (pH 2.5) and resembled intestinal mucosa (Fig. 3). In 11 cases, lining cells were tall columnar with basally located nuclei and abundant mucin which was strongly positive on alcian blue (pH 2.5) staining (Fig. 5). However there was no single cell containing argyrophil granules in tumor portion. Antral type glands were demonstrable at the valley of the tumors in 3 cases (Fig. 6).

One case of signet ring cell carcinoma showed collections of round or ovoid cells with eccentrically located nucleus and plump eosinophilic cytoplasm. On alcian blue-PAS (pH 2.5) stain, intracytoplasmic mucin was strongly PAS positive. A case classified

as mucoepidermoid carcinoma was essentially composed of solid nests of epidermoid cells in which a few acid mucin containing cells were randomly distributed. Pleomorphic spindle cell carcinoma was a type of totally anaplastic carcinoma, consisting of haphazardly arranged spindle cells with only a focus of glandular arrangement. One case of carcinosarcoma revealed two distinct histologic areas in which the one was composed of haphazardly arranged neoplastic glands in dense fibrous tissue and the other was pleomorphic spindle cell sarcoma comprising over 90% of the total mass. Between these carcinomatous and sarcomatous components, there was clear-cut interface in spite of their intimate intermingling.

Twenty three cases which contained a sufficient portion of nonneoplastic mucosa were subjected for study with reference to various metaplastic changes such as goblet cells, antral type glands, Paneth cells and argyrophil cells. The degree and extent of metaplastic change varied, but mostly their compo-

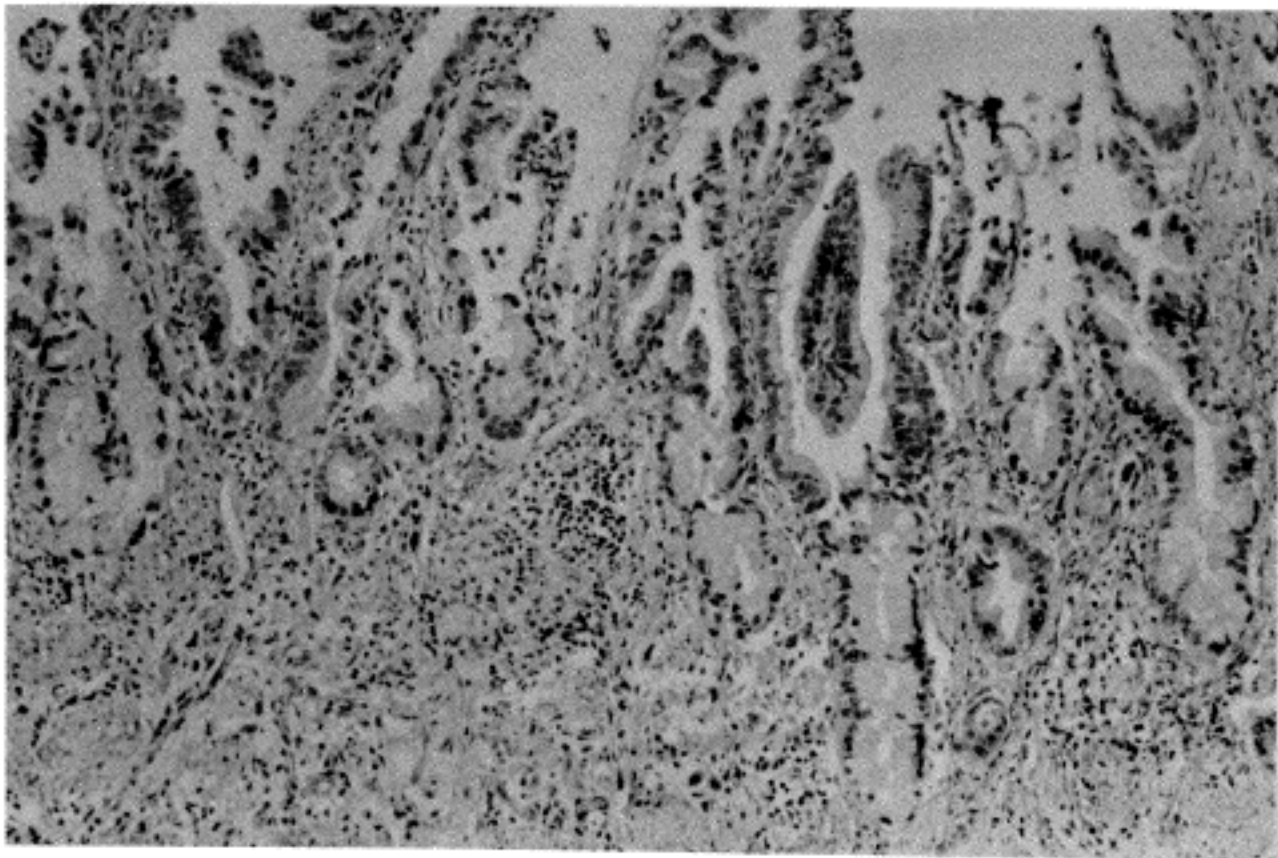


Fig. 6. Antral type metaplastic change is associated at the valley of neoplastic glands. (H&E, $\times 100$)

Table 1. Histologic classification of 34 primary carcinomas of the gallbladder

Histologic type	No. of cases
Adenocarcinoma	30 (88.2%)
Non-intestinal type	19 (55.9%)
Intestinal type	11 (32.3%)
Signet ring cell carcinoma	1 (2.9%)
Mucoepidermoid carcinoma	1 (2.9%)
Pleomorphic spindle cell carcinoma	1 (2.9%)
Carcinosarcoma	1 (2.9%)
Total	34 (100%)

Table 2. Incidences of cholelithiasis and metaplastic changes of the adjacent non-neoplastic mucosa in 34 carcinoma bearing gallbladders

Histologic type	Cholelithiasis	Metaplastic change
Adenocarcinoma	9 (26.5%)	10 (29.4%)
Non-intestinal type	3 (8.8%)	5 (14.7%)
Intestinal type	6 (17.6%)	5 (14.7%)
Signet ring cell carcinoma	1 (2.9%)	
Mucoepidermoid carcinoma		
Pleomorphic spindle cell carcinoma	1 (2.9%)	
Carcinosarcoma		
Total (34=100%)	11 (32.4%)	10 (29.4%)

nents were goblet cells and antral type glandular structure in 10 adenocarcinomas (Table 2). Of these, five of them were intestinal type adenocarcinoma.

Cholelithiasis was associated in 11 cases (32.4%), among which 6 cases were intestinal type adenocarcinoma (Table 2).

Based on gross and microscopic examination of the tumors, the growth patterns were analysed (Table 3). Fourteen cases showed villous pattern

especially in superficial portion and 19 were totally infiltrative. Out of 19 non-intestinal type adenocarcinomas, 13 (68.4%) showed infiltrative growth pattern, while 8 (72.7%) out of 11 intestinal type adenocarcinoma were papillary.

Table 3. Growth patterns of 34 primary gallbladder carcinomas by histologic type

Histologic type	Growth patterns		
	Papillary	Infiltrative	Mixed
Adenocarcinoma	14 (41.2%)	15 (44.1%)	1 (2.9%)
Non-intestinal type	6 (17.6%)	13 (38.2%)	0
Intestinal type	8 (23.6%)	2 (5.9%)	1 (2.9%)
Signet ring cell carcinoma		1 (2.9%)	
Mucoepidermoid carcinoma		1 (2.9%)	
Pleomorphic spindle cell carcinoma		1 (2.9%)	
Carcinosarcoma		1 (2.9%)	
Total (34=100%)	14 (41.2%)	19 (55.9%)	1 (2.9%)

DISCUSSION

Of the 34 cases reviewed, 30 cases (88.2%) were adenocarcinoma of various differentiation and the other four (11.8%) were unusual types of gallbladder carcinoma, three of which were first reported in Korean literatures. Classification of the gallbladder carcinoma is relatively simple, because most of the reported cases are adenocarcinoma and histologic types have been known to give less influence on prognosis⁶⁾. However, with broad review of the gallbladder carcinomas, Albores-Saavedra (1981)⁷⁾ reported 16 unusual, but characteristic types of the gallbladder.

Histology of signet ring cell carcinoma was very similar to that of the stomach, which raised a possibility of metastatic lesion to the gallbladder. But no abnormality of the stomach on operative findings and histologic features which revealed superficial spreading along the luminal surface and focal infiltration into the muscle layer were compatible to primary carcinoma of the gallbladder.

In a few organs including pancreas and upper respiratory tract, neoplastic epithelium may change its shape and growth pattern resembling stromal elements. Similar instances were described in the gallbladder and designated as pleomorphic spindle

cell carcinoma of the gallbladder⁸⁾. Most of previously reported sarcomas of the gallbladder were composed of either round or spindle and variably pleomorphic cells without any mesenchymal differentiation, but only a few were confirmed by presence of cross striation, myofibrils or fat vacuoles. Our case consisted near totally of spindle cell component and only one focus of glandular structure at the center of tumor with multiple sections. The PAS staining showed scattered cells containing PAS positive intracytoplasmic mucosubstance. Apparent transition of neoplastic glands merging with the anaplastic round or spindle cells and presence of mucin granules in cytoplasm of those anaplastic cells as in the neoplastic glands are sufficiently given for evidence of epithelial origin of this case. In differentiation of pleomorphic spindle cell carcinoma from carcinosarcoma, it is more favorable histologic features of the latter that there exist sharp transition between the epithelial and mesenchymal components and frank malignancy of both carcinomatous and sarcomatous elements. Carcinosarcoma is a rare neoplasm of the gallbladder, and only nineteen cases were reported in English literatures and one in Korea;¹⁵⁾ malignant epithelial components varied from adenocarcinoma (10 cases) and squamous carcinoma (2 cases) to other mixed types.

By its mesenchymal components the tumor was subclassified homogenous sarcoma (10 cases) and heterogenous form (9 cases)¹⁵⁻¹⁷. As in our case, no differentiation into malignant cartilage, bone or skeletal muscle seems to be more common histologic features.

Mucoepidermoid carcinoma, usually found in salivary glands or lung differs histologically from adenocarcinoma of the gallbladder in that mucus secreting cells are scattered randomly throughout; mucous cells are often quite sparse as described in our series and can be detected only when special stains are applied to reveal the presence of small intracytoplasmic mucin in cells that otherwise resemble the usual epidermoid type.

Among adenocarcinomas comprising over 80% of the gallbladder carcinoma, intestinal type is a newly designated group with reference to histologic features and histogenesis. Since Laitio¹⁸ first reported two intestinal type carcinoma of the gallbladder in 1975, several studies on its histogenesis have been referred in relation to various preceding metaplastic changes¹⁹⁻²⁰. The claim that intestinal metaplasia is a predisposing factor in histogenesis of the gallbladder carcinoma²¹⁻²³ is based on the fact that carcinoma is more frequently associated with various metaplasia, either intestinal or gastric, in the surrounding mucosa, and carcinoma itself has metaplastic characteristics. We have demonstrated a case of tubular adenoma with features of extensive metaplastic component for which a name of metaplastic variant was proposed⁵. The histologic criteria of intestinal type adenocarcinoma has not been yet firmly established, but their characteristics include variable sized glands lined predominantly by goblet cells (type I) and by tall columnar mucus secreting cells with distinct apical brush border resembling colonic crypts (type II)⁷. Paneth cells and enterochromaffin cells can be less frequently found. In three cases of intestinal type adenocarcinoma, antral type glands were found at the base of

the tumorous area. The occurrence of antral type mucous glands is observed in atrophic oxyntic mucosa, the pancreatic duct in chronic pancreatitis, normal common bile duct and normal neck portion of the gallbladder. Because these sites of lesions are vulnerable to autodigestion by acid, bile or protease, antral type mucous glands may play a protective role against various noxious stimuli. Although these glands have the same histologic appearance of gastric antral glands, there has been some debate as to whether they represent a gastric or intestinal type of metaplasia. De Boer et al²⁴, observed immunohistochemically that intestine-associated antigens were present in all type of glandular metaplasia and suggested that gastric antral type glandular and gastric superficial epithelial metaplasia were intestinal in nature. Therefore, it is assumed that the association of antral type glands with intestinal type adenocarcinoma provides further support for precursor role of intestinal metaplasia in this type of adenocarcinoma. While most adenocarcinomas of the gallbladder show focal areas of intestinal differentiation, diffuse pattern of such metaplastic change is uncommon and only three instances of intestinal type adenocarcinomas were identified in a review of 159 gallbladder carcinomas in Albores-Saavedra's series. In contrast we were able to detect 11 cases (33%) of intestinal type with scrutinizing histologic examination with assistance of mucin staining, especially alcian blue-PAS staining which revealed intracytoplasmic and extracellular mucin diffusely and strongly. It is of our experience that PAS-alcian blue staining minimize the chance of overlook of metaplastic epithelial changes.

Association with gallstones and metaplastic changes in the surrounding nontumorous mucosa is more frequent in intestinal type than in non-intestinal type ($P < 0.05$). Gallstones may play a role of irritant stimuli to the gallbladder mucosa which can be eventually reconstructed with more resistant cell type. And the subsequent increase in absorptive

capacity and accumulation of carcinogenic substance may result in malignant transformation of (reserve) cells in replication zone. At this time we can assume that association of cholelithiasis and presence of metaplastic changes are in parallel relationship in intestinal type adenocarcinoma. Intestinal type adenocarcinomas are usually papillary (72.7%) especially in superficial portion, but deeper area also shows infiltrative growth focally. This finding is comparable to intestinal type gastric carcinoma which represents frequently a polypoid and papillary growth pattern.

With these results, as in the gastric carcinoma it is strongly supported that intestinal metaplasia may play a major role as a precancerous lesion in a minor group of the gallbladder adenocarcinoma. Controlled prospective study on biological behavior of intestinal type adenocarcinoma should be followed with more cumulative cases.

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== 국문초록 ==

담낭의 원발성 암종

—화생성 변화와의 상관 관계를 중심으로한
34 담낭절제례 분석—

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담낭암의 대부분은 선암종으로 그 병리학적 유형이 다양하지 않으며 임상적으로도 조직학적 분화도보다는 암종의 침습도가 예후에 큰 영향을 미치는 것으로 알려져 있다. 따라서 담낭의 원발성 암종의 병리조직학적 기술은 오랫동안 큰 변화가 없었으나 최근에는 담낭암의 발생기원 측면에서 장형화생과의 연관성이 대두되었으며 암종내의 장형화생의 조직소견을 보이는 선암종중 일부를 장형 선암종이라 명하고 이들의 병리조직학적 소견 및 비종양성 담낭 점막의 장형화생과의 관련성이 추구된 바

있다.

저자들은 1980년부터 1986년까지 7년간 서울대학교병원에서 외과적으로 절제된 34예의 원발성 담낭암종을 종양 및 비종양성 점막의 화생성 변화에 중점을 두고 병리학적으로 재검색 하였다.

34예중 30예(88.2%)가 선암종이었으며 이중 11예는 장형선암종으로서 빈번한 배상세포와 더불어 점액을 분비하는 원주형 세포로 이루어져 있어 대장 점막과 유사하였다. 또한 기질 및 종양세포질내 점액은 대부분이 산성점액이었으며 주변 비종양성 점막에서도 화생성 변화가 비장형 선암종의 경우에서 보다 빈번히 관찰되었다. 이상의 소견은 장형화생이 위암종의 경우와 마찬가지로 전암성 병변으로서 일부 담낭암종의 발생에 관여하리라는 가설을 뒷받침 한다고 사료된다.

담석은 34예중 11예에서 수반되었으며 이중 6예가 장형화생성 선암종이었다. 이러한 사실은 장형선암종의 경우에는 지속적 점막 자극이 화생성 변화를 유도하며 이를 바탕으로 선암종이 발생할 가능성을 시사하고 있으며 그 기전을 추정하였다.

그 외의 2예는 지금까지 국내 문헌상 보고된 바 없는 희귀 유형의 원발성 담낭암종인 인환 세포암, 점액—유상피종이었으며 나머지 2예는 각각 미분화 암종의 한 유형인 미분화성 방추세포 암종과 암육종이었다.