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Carcinoma of the gallbladder: the correlation between histogenesis and prognosis

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Summary. Ninety-two cases of adenocarcinoma of the gallbladder were classified into the metaplastic or non-metaplastic type, based on the presence or absence of metaplastic changes in the tumour tissues. The differences in biological characteristics were compared between these tumour types. The metaplastic type was more common than the non-metaplastic type in females and the survival rate in this type was better than that in the non-metaplastic type. The modes of tumour spread also differed, the metaplastic type frequently showed lymphatic metastasis, whereas the non-metaplastic type often metastasized by direct invasion. The difference in prognosis might be explained by the different modes of tumour spread. This classification corresponded well to that of gastric carcinoma into intestinal type and diffuse type and the results suggest that it might provide a basis for evaluating various aspects of gallbladder carcinoma.

Key words: Gallbladder carcinoma – Metaplasia – Prognosis – Histogenesis

Introduction

The normal gallbladder mucosa is characterized by a relatively simple structure composed of a single layer of uniform columnar epithelium except for the presence of mucous glands in the neck region. However, metaplastic changes are not infrequently observed in chronic cholecystitis (Christie 1954; Hospes 1959; Delaquerriere et al. 1962; Järvi and Laurén 1967; Laitio 1975, 1980; Tsutsumi et al. 1984).

Metaplastic changes in the gallbladder include various changes such as the occurrence of goblet cells, Paneth cells, pseudo-pyloric glands, and endocrine cells. Recently, van den Oord et al. (1983) reported that immunoreactive lysozyme, which is not present in normal gallbladder mucosa, is present in the pseudo-pyloric glands of the gallbladder. They suggested that lysozyme immunoreactivity may serve as an indicator of functional metaplasia of the gallbladder. We have examined the incidences of lysozyme immunoreactivity and endocrine cells, together with goblet cells, Paneth cells and pseudo-pyloric glands in the gallbladder of the fetus, the normal adult and in cholecystitis. We concluded that these two markers are the most useful common indicators of gastrointestinal metaplasia of the gallbladder (Yamamoto et al. 1986).

The aetiology of gallbladder carcinoma remains unknown, but it is also well known that metaplastic changes are frequently observed not only in tumour and adjacent non-tumour tissues of carcinomas (Laitio 1976, 1983; Azadeh and Parai 1980; Sato et al. 1983) but also in dysplastic mucosa (Albores-Saavedra et al. 1980; Laitio 1983; Dowling and Kelly 1986; Yamagiwa 1987) and adenomas (Christensen and Ishak 1970; Sato et al. 1985; Yamamoto et al. 1988) which may be precursor lesions of gallbladder carcinoma. Therefore, some authors have considered that metaplastic changes play an important role in the histogenesis of gallbladder carcinoma.

Recently, we, in examining the epithelial polypoid lesions of the gallbladder histologically and immunohistochemically, showed that these lesions could be classified into two types according to the characteristics of the epithelium composing the polypoid lesions. One is derived from ordinary epithelium of the gallbladder mucosa without metaplastic changes and the other from metaplastic epithelium. The adenomas were subclassified into ordinary type adenoma consisting of ordinary epithe-

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lium without metaplasia and into metaplastic type adenoma consisting of metaplastic epithelium (Yamamoto et al. 1988). These findings have led to a hypothesis that various epithelial diseases of the gallbladder can be classified into two groups, one being derived from ordinary and the other from metaplastic epithelium (Yamamoto et al. in press). Based on this hypothesis, gallbladder carcinomas were divided into metaplastic type and non-metaplastic type according to the presence or absence of metaplastic markers such as endocrine cells and lysozyme immunoreactivity in the tumour tissues, and the prognosis of each type of carcinoma was compared in order to examine the usefulness of this classification.

Materials and methods

Ninety-two cases of adenocarcinoma of the gallbladder were used in this study, which were selected from the files of our department and Hiroshima Prefectural Tumor Registry Committee. In all these cases which underwent cholecystectomy or some more extensive operation, the operative findings and follow up data could be obtained. Cases who died within 1 month after the operation were excluded from this study.

Macroscopically, the tumours were classified into papillary, nodular and flat type based on the features of tumour surface. Finely granular surfaced tumours were included in flat type.

Histologically, formalin-fixed and paraffin-embedded specimens were cut into 4 μm sections, which were stained with haematoxylin and eosin, Grimelius technique for argyrophil reaction, and peroxidase-antiperoxidase method for lysozyme-immunoreactivity, as described in detail elsewhere (Yamamoto et al. 1986).

According to the histological typing of tumours of the liver, biliary tract, and pancreas (Gibson 1978), the cases were classified into well-, moderately-, and poorly-differentiated adenocarcinoma and mucinous adenocarcinoma. Moreover, the cases were also divided into non-metaplastic type and metaplastic type, based on the presence or absence of metaplastic markers such as argyrophil cells and lysozyme immunoreactivity in the tumour tissues.

The stages of gallbladder cancer were classified into four groups, that is, stages I, II, III, and IV according to the TNM classification (Hermanek and Sobin 1987).

The survival curves were calculated by Kaplan and Meier's method. Differences in survival curves were measured using the generalized Wilcoxon test. In order to determine the independent contribution of each factor to prognosis multivariate analyses were undertaken using the Cox proportional hazards model (statistical program P2L of the BMDP library) (Dixon 1983). The prognostic factors examined in this study were as follows: sex, age, stages, operative procedures (2 groups; local resection including cholecystectomy and wedge resection of gallbladder bed, more extended operation), histological types, and tumour types (2 groups; non-metaplastic type, metaplastic type).

Moreover, the degree of pseudo-pyloric gland metaplasia in the gallbladder mucosa adjacent to carcinoma was compared among the tumour types in an attempt to elucidate histogenesis. The degree was scored 0 to 3; that is, 0, no metaplasia; 1, focal; 2, intermediate; and 3, diffuse.

Results

Sixty-eight of the 92 patients were females with a female to male ratio of 2.8:1. The average age of the patients at the time of operation was 64.5 years. Stones were present in 56 (62.2%) of 90 patients. In 2 other cases, no data were available about gallstones. The operative procedures employed are listed in Table 1. Macroscopically, they were divided into 30 cases of papillary type, 39 cases of nodular type, and 23 cases of flat type. Histologically, they were classified into 63 cases of well-differentiated adenocarcinoma, 17 cases of moderately-differentiated adenocarcinoma, 11 cases of poorly-differentiated adenocarcinoma, and one case of mucinous adenocarcinoma. By stage, they were divided into 15 cases of stage I, 26 cases of stage II, 26 cases of stage III, and 25 cases of stage IV.

As to the presence of metaplastic markers in tumour tissues, 47 cases (51.1%) of the 92 carcinomas contained argyrophil cells and 58 cases (63.0%) showed lysozyme-immunoreactivity. Based on the presence or absence of metaplastic markers in the tumour tissues, these 92 cases were divided into 24 cases (26.1%) showing no metaplasia (Fig. 1) and 68 cases (73.9%) showing at least one of the markers of metaplasia (Fig. 2). In this study, we called the former the non-metaplastic type and the latter the metaplastic type. The clinicopathological comparison between the non-metaplastic type and the metaplastic type of gallbladder carcinoma is summarized in Table 2.

The female to male ratio of 3.5 in metaplastic type carcinoma was higher than that of 1.7 in non-metaplastic type. The average age was not different between the two types. The frequency of cholelithiasis in the metaplastic type was slightly higher than that in the non-metaplastic type, but the difference was not significant. The macroscopic features were not different between the two types. As to the relationship between tumour types and degree of differentiation, well-differentiated carcinomas tended to be more common in the metaplastic type, but moderately or poorly differentiated carcinomas were more frequent in the non-metaplastic type. There was no significant difference in stage between the tumour types.

The five-year survival rate for the total was 36.8%. The survival curves for all patients by stages are shown in Fig. 3. The differences in survival rates by the generalized Wilcoxon test were significant ($p < 0.01$) between stage II and stage III, and stage III and stage IV, but not between stage I and stage II. The survival curves for patients in

Table 1. Operative procedures

		No. of cases
Cholecystectomy only		63
Cholecystectomy	+ wedge resection of gallbladder bed	16
Cholecystectomy	+ choledocochectomy	4
Cholecystectomy	+ wedge resection of gallbladder bed + choledocochectomy	4
Cholecystectomy	+ wedge resection of gallbladder bed + pancreato-duodenectomy	2
Cholecystectomy	+ choledocochectomy + pancreato-duodenectomy	1
Cholecystectomy	+ choledocochectomy + right hepatic lobectomy	1
Cholecystectomy	+ choledocochectomy + pancreato-duodenectomy + right hepatic lobectomy	1

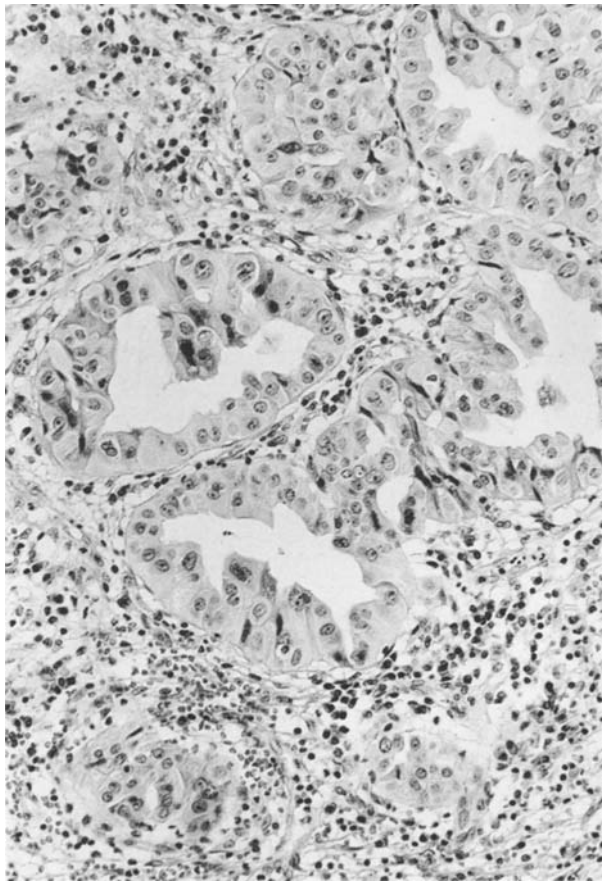

Fig. 1. Histological appearance of a case of non-metaplastic type adenocarcinoma

all stages of non-metaplastic and metaplastic types of gallbladder carcinoma are shown in Fig. 4. The metaplastic type showed a better survival rate than the non-metaplastic type with a statistically significant difference. The survival curves of non-metaplastic type and metaplastic type carcinomas in stage III are shown in Fig. 5. The patients of the metaplastic type showed a better survival rate than the non-metaplastic type, but there was no significant difference. In comparing the survival rates for patients in stages III and IV, the difference in prognosis between the tumour types became more apparent (Fig. 6).

The Cox proportional hazards model was used to study the prognostic influence of possible various factors on survival. The results of analysis in all cases of gallbladder adenocarcinoma are shown in Table 3. Only the stage proved to be of prognostic significance. Then, the Cox analysis was made using the cases of stages III and IV (Table 4). The only factor of prognostic significance proved to be the tumour type.

As a difference in prognosis was observed between tumour types, the modes of spread were examined. The modes of metastatic spread in the 51 cases of stages III and IV are compared between the tumour types in Table 5. The incidence of lymphatic metastasis to regional lymph nodes in the metaplastic type carcinoma was higher than that in the non-metaplastic type carcinoma. However, the non-metaplastic type carcinomas more frequently showed direct invasion into the omentum and gastro-intestinal tract through the serosa of the gallbladder than did the metaplastic type (with a statistically significant difference ($p < 0.05$) by χ^2 test).

In 73 of the 92 cases of gallbladder carcinoma, it was possible to investigate the non-neoplastic mucosa adjacent to carcinoma. The mean score of metaplasia in the non-neoplastic mucosa of the metaplastic type carcinoma was 2.18 when compared with 1.59 for the non-metaplastic carcinoma. The difference between the two was significant by the t-test ($p < 0.05$).

Discussion

In this study, gallbladder adenocarcinomas were divided into metaplastic type and non-metaplastic type according to the presence or absence of metaplastic markers in the tumour tissues. This study confirmed that there were several differences in biological characteristics between the tumour types, the most important of which was their prognosis. The metaplastic type carcinoma had a better prog-

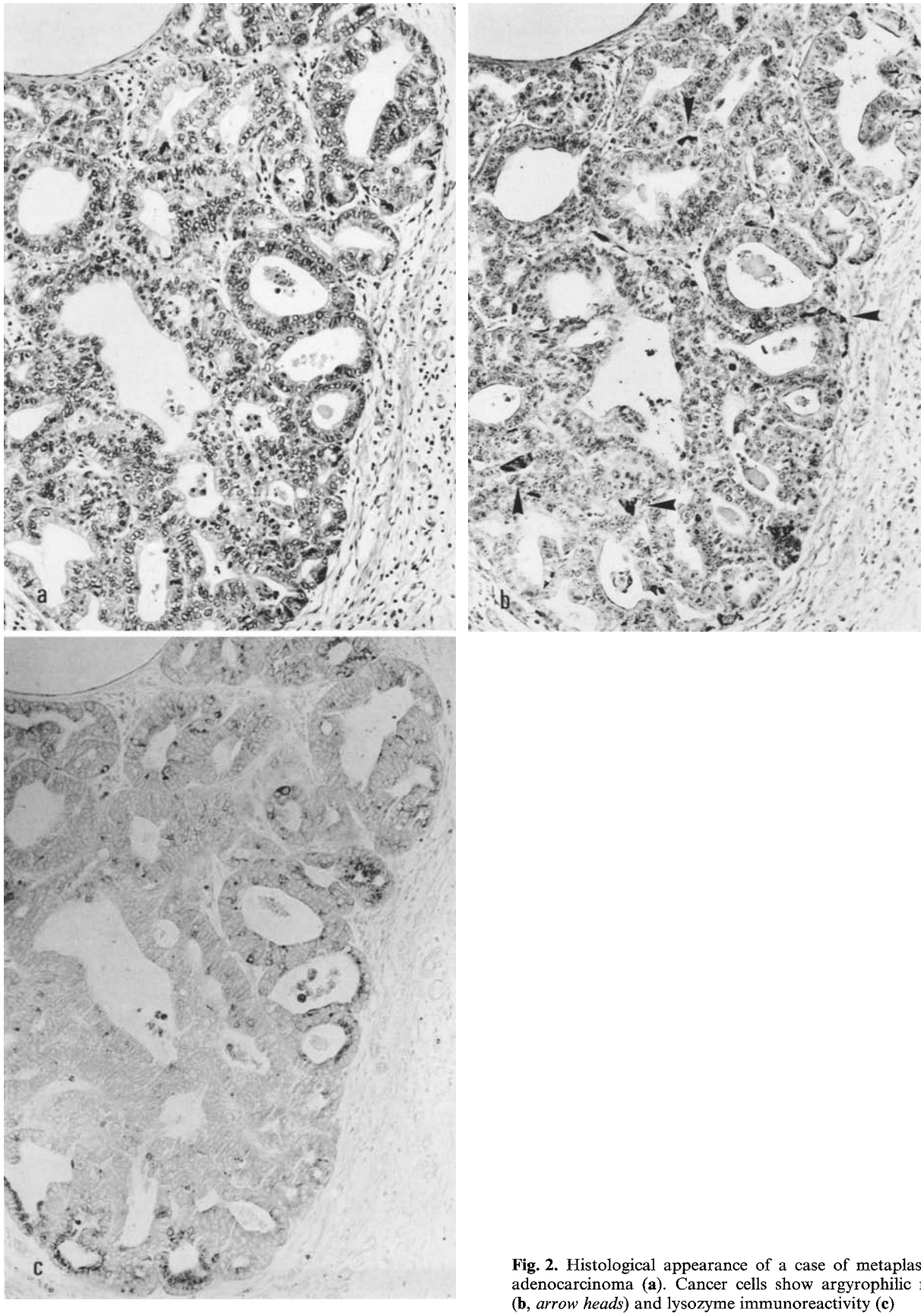

Fig. 2. Histological appearance of a case of metaplastic type adenocarcinoma (**a**). Cancer cells show argyrophilic reaction (**b**, *arrow heads*) and lysozyme immunoreactivity (**c**)

Table 2. Comparison of clinicopathological findings between non-metaplastic type and metaplastic type carcinoma

	Non-metaplastic type	Metaplastic type
No. of cases	24 cases	68 cases
Male to female ratio	9:15	15:53
Mean age	65.1 years	64.3 years
Cholelithiasis	54.2%	63.6%
Macroscopic type		
papillary	7 cases (29.2%)	23 cases (33.9%)
nodular	12 cases (50.0%)	27 cases (39.7%)
flat	5 cases (20.8%)	18 cases (26.4%)
Histological type		
well*	10 cases (41.7%)	53 cases (77.9%)
moderately*	9 cases (37.5%)	8 cases (11.8%)
poorly	5 cases (20.8%)	6 cases (8.8%)
muc	0	1 case (1.5%)
Stage		
I	5 cases (20.8%)	10 cases (14.7%)
II	5 cases (20.8%)	21 cases (30.9%)
III	5 cases (20.8%)	21 cases (30.9%)
IV	9 cases (37.5%)	16 cases (23.5%)

* $p<0.01$, χ^2 test

well, well differentiated adenocarcinoma; *moderately*, moderately differentiated adenocarcinoma; *poorly*, poorly differentiated adenocarcinoma; *muc*, mucinous adenocarcinoma

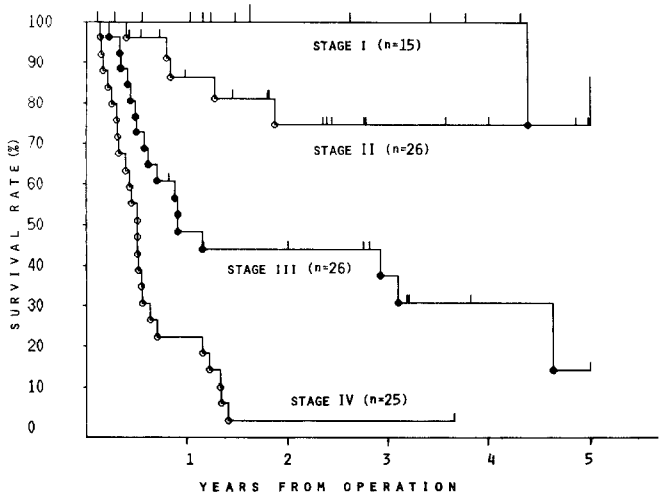

Fig. 3. Survival curves by stages

nosis than the non-metaplastic type carcinoma in comparing the survival rates of the patients in all stages, and stages III and IV by the generalized Wilcoxon test. Moreover, the Cox analysis showed that the tumour type proved to be a significant prognostic factor. The modes of spread of carcinoma were also different between the types. The metaplastic type frequently showed lymphatic metastasis, whereas the non-metaplastic type often me-

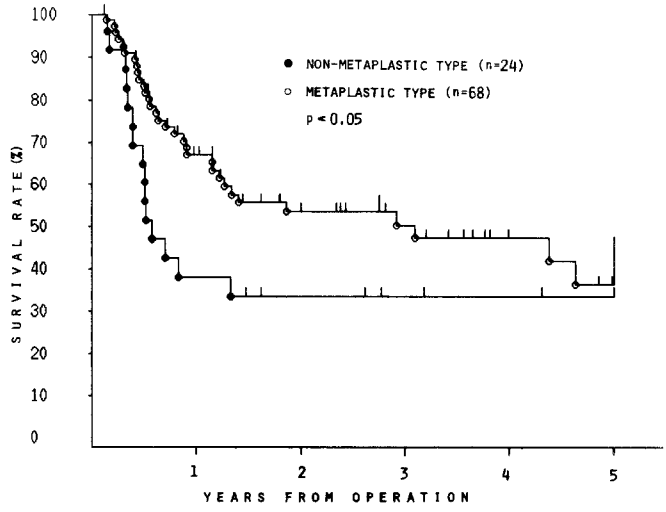

Fig. 4. Survival curves of metaplastic type and non-metaplastic type of gallbladder carcinoma in all cases

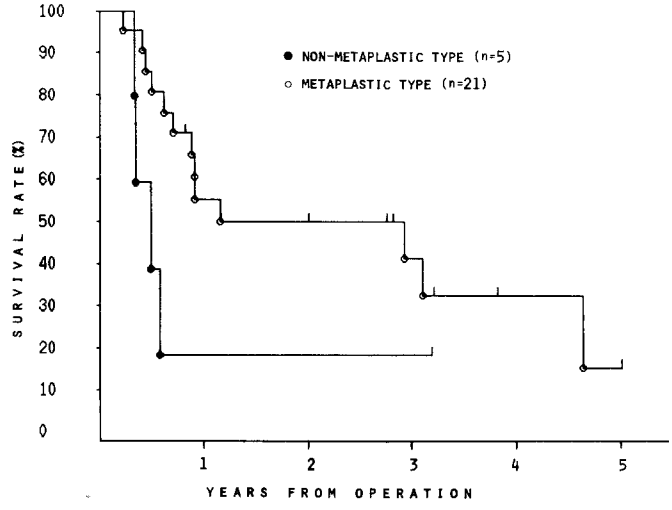

Fig. 5. Survival curves of metaplastic type and non-metaplastic type of gallbladder carcinoma in stage III

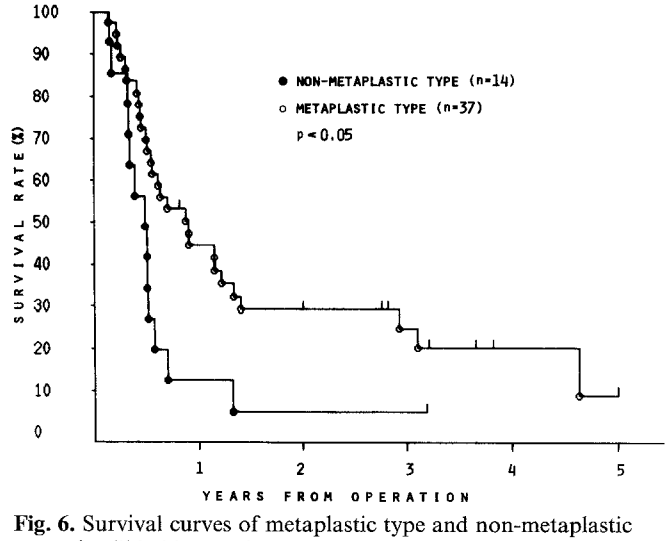

Fig. 6. Survival curves of metaplastic type and non-metaplastic type of gallbladder carcinoma in stages III and IV

Table 3. Cox proportional hazards model in all cases of gallbladder adenocarcinoma

Variable	Coefficient	Coefficient/SE	*p* value
Sex	−0.4741	−1.2817	0.194
Age	−0.0273	−1.9237	0.054
Stage	1.2304	5.9227	0.000
Operative procedure	−0.0962	−0.2229	0.823
Histological type	0.0161	0.0804	0.935
Tumour type	−0.5133	−1.4200	0.155

SE: Standard error

Table 4. Cox proportional hazards model in stages III and IV of gallbladder adenocarcinoma

Variable	Coefficient	Coefficient/SE	*p* value
Sex	−0.4755	−1.1691	0.242
Age	−0.0252	−1.7118	0.086
Operative procedure	−0.0700	−0.1593	0.873
Histological type	−0.1135	−0.5325	0.594
Tumour type	−0.9286	−2.3406	0.019

SE: Standard error

Table 5. The modes of spread of tumours in each type of carcinoma

Modes of spread	Non-metaplastic type	Metaplastic type
	14 cases	37 cases
Lymphatic	5/ 8 (62.5%)	26/31 (83.9%)
Hematogenous	4/13 (30.8%)	3/33 (9.1%)
Direct invasion		
to omentum, G-I tract*	6/13 (46.2%)	6/34 (17.6%)
liver	5/13 (38.5%)	9/34 (26.5%)
wall of extra-hepatic bile duct	7/14 (50.0%)	15/34 (44.1%)

* $p<0.05$, χ^2 test

Each denominator indicates the number of cases examined

tastasized by direct invasion into the neighboring organs in the peritoneal cavity. The difference in prognosis observed may be dependent upon these different modes of spread of gallbladder carcinoma.

The histogenesis of gallbladder carcinoma is unknown. However, the results of our previous pathological studies on the epithelial diseases of the gallbladder have led to a hypothesis that there are at least two histogeneses for gallbladder carcinoma, one type being derived from ordinary epithelium and the other from metaplastic epithelium (Yamamoto et al. 1988; Yamamoto et al. in press). The presence or absence of metaplasia in tumour tissues was used as a marker which differentiated these two types of carcinoma. There is a possibility that the metaplastic changes in tumour tissues are secondary phenomenon associated with the progression of the tumour. We therefore, compared the frequency of metaplastic changes between early carcinoma and advanced carcinoma in order to determine whether or not the metaplastic changes increased as the tumour progressed. However, no differences could be demonstrated between the stages. This finding indicated that the metaplastic changes in the tumour tissues might be a phenotypic expression of the original tissues from which they were derived rather than a secondary phenomenon associated with progression (Yamamoto et al. in press). These results indicated that the metaplastic type carcinoma in this study was consistent with carcinoma derived from metaplastic epithelium. However, it is difficult to determine the origin of the non-metaplastic type carcinoma. In this study and our previous report (Yamamoto et al. in press) we showed that the non-metaplastic type carcinoma was often surrounded by an ordinary mucosa without (or with mild) metaplastic changes. Metaplastic type tumours were frequently surrounded by a metaplastic mucosa. Moreover, we have found a residum of ordinary epithelium without atypia within the tumour tissue of non-metaplastic type carcinomas (Yamamoto et al. in press). These findings suggested that most of the non-metaplastic type carcinomas in this study might be consistent with carcinoma derived from ordinary epithelium, although the possibility could not be completely denied that some carcinomas derived from metaplastic epithelium might be included in the non-metaplastic type because of the loss of phenotype of the original tissues associated with malignant change.

To pursue an analogy, it is evident that gastric carcinomas can be divided into types, the intestinal and the diffuse types (Laurén 1965), the expanding and the infiltrative types (Ming 1977), or the differentiated and undifferentiated carcinoma (Nakamura et al. 1969). With regard to the histogenesis of gastric carcinoma, Nakamura et al. (1969) have suggested that the differentiated carcinoma is derived from intestinalized mucosa and the undifferentiated carcinoma from ordinary gastric mucosa. It has been also recognized that there are various differences between these two types of gastric carcinoma in histological structure, growth pattern, sex and age of the patients, and also in survival rates. The proportion of men and older patients is greater in the intestinal or expanding type than in the dif-

fuse or infiltrative type. In the surrounding mucosa the incidence and degree of intestinal metaplasia are greater in the intestinal type carcinoma. The prognosis is poorer in the diffuse type than in the intestinal type carcinoma (Laurén 1965; Stemmermann and Brown 1974; Ming 1977).

There are thus some similarities between gastric and gallbladder adenocarcinoma in so far as there are histogenetically different two types, one being derived from ordinary epithelium and the other from metaplastic epithelium, and each of them has different biological characteristics. It is interesting to compare the relationship between tumour types and biological characteristics in gallbladder carcinoma with that in gastric carcinoma. The metaplastic type gallbladder carcinoma corresponds well with the intestinal type gastric carcinoma in showing a significant difference of sex distribution, associated metaplasia in adjacent mucosa to carcinoma, and having a better prognosis. As to the sex distribution, the metaplastic type of gallbladder carcinoma is more common in females, whereas the intestinal type of gastric carcinoma is more frequent in males. This difference of sex distribution may be dependent upon the sex difference in the frequency of metaplastic changes between the gallbladder and stomach (Kozuka and Hachisuka 1984). However, the non-metaplastic type of gallbladder carcinoma has common characteristics with the diffuse type of gastric carcinoma in having no apparent sex distribution bias, being surrounded by non-metaplastic mucosa, and having a poorer prognosis.

In this study, gallbladder carcinomas were classified into metaplastic type and non-metaplastic tpye, and this classification was found to be well correlated with the biological behavior and may reflect the histogenesis of gallbladder carcinoma. The recognition that there are two different types of carcinoma in the gallbladder will facilitate future studies and promote a better understanding of this disease.

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