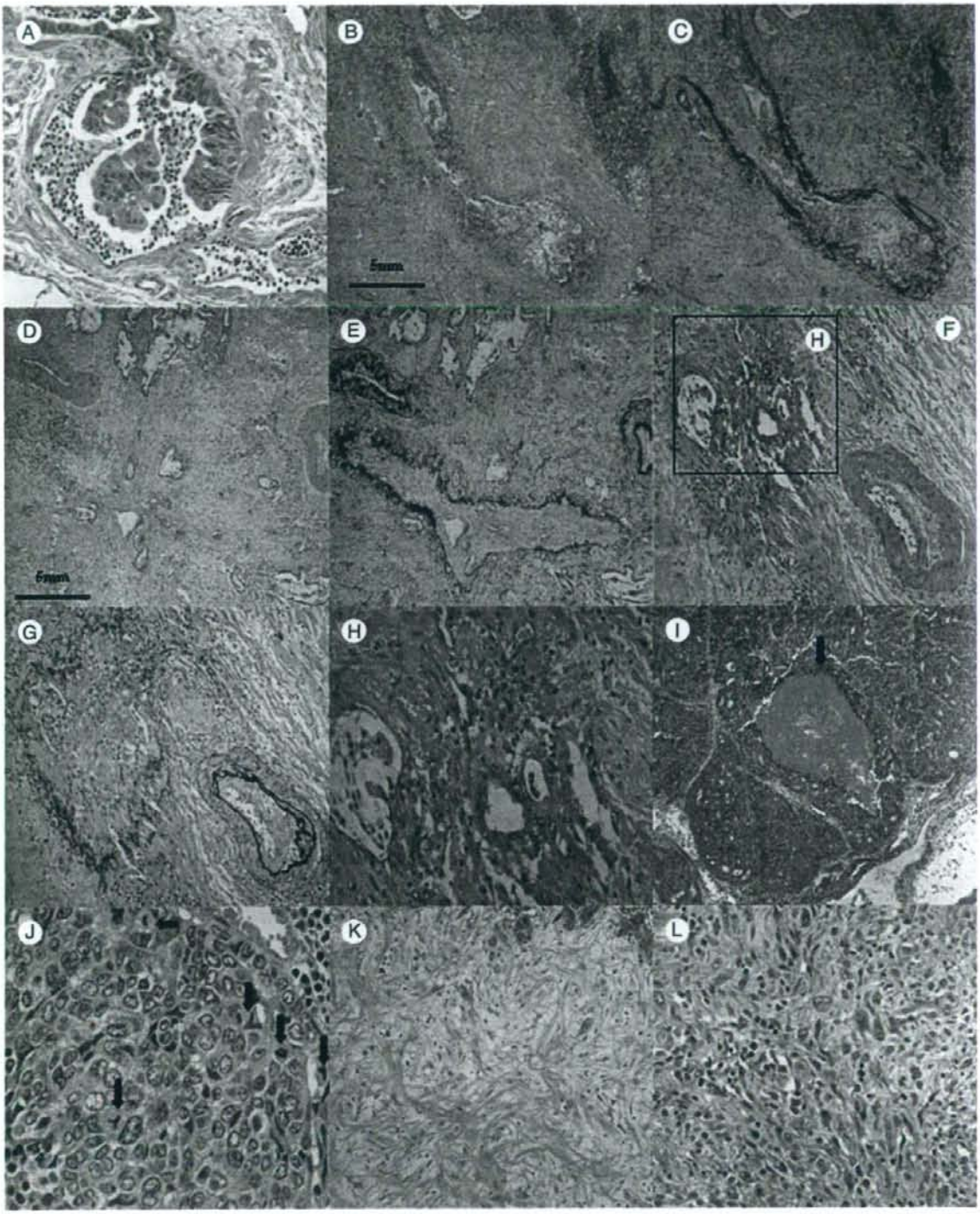

A
B
C
D
E
F
H
G
H
I
J
K
L

Table 1 PVN classification of patient with EBDC

Parameters	Score
1. Depth of invasion of the primary tumors	
Carcinoma in situ/fm/ss *vs* bs	0 *vs* 1
2. Nuclear atypia of tumor cells in lymph vessel	
Mild/moderate *vs* severe	0 *vs* 1
3. Angiomatous stroma of blood vessel tumor emboli	
Absent *vs* present	0 *vs* 1
4. Size of blood vessel tumor emboli (mm)	
Absent/≤1.7 *vs* >1.7	0 *vs* 1
5. Fibrosis grade of blood vessel tumor emboli	
None/scant/moderately abundant *vs* abundant	0 *vs* 1
6. No. of mitotic figures in nodal metastatic tumors (/1 high-power field)	
N0/≤4 *vs* >4	0 *vs* 1
7. Tumor necrosis in nodal metastatic tumors	
N0/absent *vs* present	0 *vs* 1
8. Fibrosis grade of tumor stroma in nodal metastatic tumors	
N0/none/scanty/moderately abundant *vs* abundant	0 *vs* 1
9. Fibroblasts with a conspicuous cytoplasm in nodal metastatic tumors	
N0/inconspicuous *vs* conspicuous	0 *vs* 1 Total: 0-9
Classes of PVN classification	
Low	N0 and score 0
Intermediate	N0 and score 1 or 2 N+ and score 0-3
High	N0 and score 3 or more N+ and score 4 or more

Abbreviations: N0, lymph node negative; N+, lymph node positive; fm, fibromuscular layer; ss, subserosa; bs, beyond serosa.

The pathological tumor-node-metastasis (pTNM) classification is the histologic prognostic classification currently used clinically worldwide to predict the outcome of patients with EBDC [1]; however, several studies have reported that it is not useful for predicting the outcome [2-5]. The Japanese pTNM (JpTNM) classification is a histologic prognostic classification for the outcome of patients with EBDC [6] that is based on the histologic features of the primary tumor (T category), nodal status (N category), and the presence or absence of distant organ metastasis, the same as the pTNM classification. Because the JpTNM system is similar to the pTNM system, except for minor differences in the definition of the T category and N category, the JpTNM system also lacks definitive power for predicting the outcome, thereby making it necessary to devise a system that would more accurately predict the outcome of patients with EBDC.

We recently established a new histologic prognostic classification for invasive ductal carcinoma of the breast, the primary tumor/vessel tumor/nodal tumor (PVN) classification, based on some of the histologic characteristics of tumor cells in the vessels and lymph nodes of patients with invasive ductal carcinoma of the breast; and we confirmed that the PVN classification is better than better known histologic prognostic classifications of invasive ductal carcinoma of the breast [7]. The same as in patients with invasive ductal carcinoma of the breast, we have confirmed that the histologic characteristics of tumor cells and tumor stromal cells in the lymph vessels, blood vessels, and lymph nodes of patients with EBDC are more strongly associated with tumor recurrence or death than the characteristics of the primary tumors independent of nodal status or tumor location of EBDC [8]. We therefore predicted that a PVN classification of EBDC based on the histologic characteristics identified in an overall evaluation of tumor cells and tumor stromal cells in primary invasive tumors, vessels, and lymph nodes would be the best prognostic histologic classification for predicting patient outcome.

Hong et al recently reported using the new sixth edition of the American Joint Committee on Cancer (AJCC) classification [9] to predict the outcome of patients with EBDC [10]. The purpose of the present study was to establish a PVN classification for EBDC to be able to more accurately predict the outcome of patients with EBDC and to compare the prognostic power of the PVN classification with that of the pTNM, the AJCC, and the JpTNM classifications.

2. Materials and methods

2.1. Patients

Between July 1992 and December 2004, 96 consecutive patients with EBDC were surgically treated at the National

Fig. 1 Histologic characteristics of tumor cells and tumor stromal cells evaluated in the PVN classification. A, Tumor cell nests in lymph vessels lined by endothelial cells and filled with lymphocytes. Tumor cells with large nuclei of various sizes. B and C, Large blood vessel tumor embolus with supporting elastic fibers. D and E, Tumor cells with tubular features and an abundant fibrous stroma in the lumen of a blood vessel with supporting elastica. F to H, The angiomatous stroma of the blood vessel tumor embolus supported by elastic fibers consists of many microvessels intermingled with fibroblasts. I, Necrosis in a nodal metastatic tumor (arrow). J, Several mitotic figures can be seen in nodal metastatic tumor cells (arrows). K, Nodal metastatic tumor with an abundant fibrous stroma and stromal fibroblasts exhibiting a storiform pattern. L, Tumor stromal fibroblasts intermingled with tumor cells containing prominent basophilic or amphophilic cytoplasm.

Cancer Center Hospital East. The 24 patients who died within 1 month of surgery were excluded because their cause of death was thought to be related to surgery. The remaining 72 patients were enrolled as the subjects of this study. Clinical information was obtained from the patients' medical records after a thorough and complete histologic examination of all of the EBDCs. All patients were Japanese (47 men, 25 women), and they ranged in age from 41 to 81 years (mean, 65 years). All patients had a solitary lesion. Subtotal stomach-preserving pancreaticoduodenectomy, pylorus-preserving pancreaticoduodenectomy, or pancreaticoduodenectomy was performed in the 35 patients whose EBDC was located in the distal or middle portion of the extrahepatic bile duct; and hepatectomy plus pancreaticoduodenectomy or a right- or left-hepatectomy was performed in the 37 patients whose EBDC was located in the hilar potion. Lymph node dissection was performed in all patients. None of the patients had received radiotherapy or chemotherapy before surgery, but 7 patients received adjuvant therapy after surgery. For pathological examination, the surgically resected specimens were fixed in 10% formalin overnight at room temperature. The size and gross appearance of the tumors were recorded, and tumor size was confirmed by comparison with tumor size measured on the histologic slides. The entire tumor was cut into slices at intervals of 0.5 to 0.7 cm, and all tumor-containing sections were routinely processed and embedded in paraffin to examine their histologic characteristics. Serial sections of each tumor area were cut from the paraffin blocks. One section was stained with hematoxylin and eosin and examined histologically to confirm the diagnosis. Elastica staining was performed on another section to assess blood vessel invasion in all cases; and if tumor cell nests were observed in vessels lined by endothelium that possessed supporting smooth muscle or elastica, the tumor was recorded as "blood vessel invasion." We examined all of the tumor areas under midpower magnification to evaluate them for the presence of blood vessels that had been invaded by tumor cells (Fig. 1B-H). The section with the largest surface area cut from each of the lymph nodes that had been dissected was examined histologically to determine whether lymph node metastasis had occurred.

One author (T. H.) assessed all of the histologic characteristics of the tumors, and another author (O. A.) identified the histologic characteristics of the tumors to confirm the tumor cell characteristics assessed by the first author (T. H.). Whenever a discrepancy occurred, the 2 authors reexamined the slides together to reach a consensus.

2.2. Proposed PVN classification

The PVN classification for EBDCs was devised based on the histologic characteristics of the tumors that were found to be most important for predicting the outcome of patients with EBDC in a previous study [8]. The parameters of the PVN classification for patients with EBDC are listed in Table 1. The methods used to assess each parameter have been described in the previous article [8]. In brief, tumor cell nests in vessels lined by endothelium with no supporting smooth muscle or elastica were defined as *lymph vessels invaded by tumor cells* (Fig. 1A); and the tumor cells in the lymph vessels were examined for nuclear atypia (mild, moderate, severe). We defined tumor cell nests in vessels lined by endothelium that had supporting smooth muscle or elastica as *blood vessels invaded by tumor cells*. The largest diameter of the largest tumor embolus in a blood vessel was measured under a microscope equipped with a ×10 eyepiece containing a graticule, and blood vessel tumor emboli were examined for degree of tumor stroma (none, scanty, moderately abundant, abundant) (Fig. 1B-E). A blood vessel tumor embolus with an angiomatous stroma was defined as *a blood vessel tumor embolus whose stroma contains ample microvessels* (Fig. 1F-H). Tumor necrosis was defined as *present* in a nodal metastatic tumor when it contained necrosis that was visible under low-power magnification (×2 or ×4 objective, and ×10 ocular) (Fig. 1I). Tumors containing necrosis that was hard to see under low-power magnification and tumors that contained no necrosis were defined as tumor necrosis *negative*. Tumor areas in which many tumor cells throughout the entire area contained mitotic figures were randomly searched under medium power (×10 or ×20 objective, and ×10 ocular), and the area with the greatest number of tumor cell mitotic figures in a single high-power field (×40 objective and ×10 ocular) was selected to count the number of mitotic figures in each case (Fig. 1J). The degree of tumor stroma was classified as follows: (1) none, when there was no obvious fibrous stroma; (2) scanty, when 50% or less of the entire tumor area consisted of fibrous stroma; (3) moderately abundant, when 50% to 80% of the entire tumor area consisted of fibrous stroma; and (4) abundant, when more than 80% of the entire tumor area consisted of fibrous stroma (Fig. 1K). We noted that some tumors contained tumor stromal fibroblasts containing abundant basophilic or amphophilic cytoplasm that made them clearly distinguishable from the surrounding collagen fibers composing the tumor stroma (Fig. 1L). If such cells were frequently observed within a tumor, the tumor was classified as containing tumor stromal fibroblasts with conspicuous cytoplasmic features. The nuclei of some of tumor stromal fibroblasts with conspicuous cytoplasmic features contained prominent nucleoli that were larger than the nucleoli in the tumor stromal fibroblasts whose cytoplasm was inconspicuous.

In the PVN classification of EBDC (Table 1), a score of 1 point was assigned for each of the following: depth of invasion beyond the serosa by the primary tumor, severe nuclear atypia of tumor cells in lymph vessels, presence of an angiomatous stroma in blood vessel tumor emboli, blood vessel tumor embolus greater than 1.7 mm in diameter, presence of an abundant fibrous stroma in blood vessel tumor

Table 2 Crude disease-free survival and overall survival for PVN, pTNM, AJCC, and JpTNM classifications in all patients with EBDC

Classifications					
PVN					
Classes	Cases	TRR (%)	*P*	MR (%)	*P*
Low	12	2 (17)		1 (8)	
Int	30	19 (63)	.002	18 (60)	<.001
High	30	30 (100)	<.001	29 (97)	<.001
Total	72	51		48	
pTNM					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
IA	13	6 (46)		5 (38)	
IB	3	0	.549	0	.633
IIA	6	4 (67)	.198	4 (67)	.198
IIB	37	28 (76)	.370	26 (70)	.564
III	13	13 (100)	.103	13 (100)	.108
Total	72	51		48	
AJCC					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
IA	14	6 (43)		5 (36)	
IB	2	0	.663	0	.707
IIA	11	6 (55)	.414	6 (55)	.491
IIB	40	35 (88)	.012	34 (85)	.025
III	5	4 (80)	.972	3 (60)	.267
Total	72	51		48	
JpTNM					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
I	5	0		0	
II	14	7 (50)	.065	6 (43)	.138
III	28	21 (75)	.032	20 (71)	.012
IVa	16	14 (88)	.667	13 (81)	.605
IVb	9	9 (100)	.239	9 (100)	.044
Total	72	51		48	
Multivariate analyses					
Classifications		Disease-free survival Trend HRs/95% CIs/*P*		Overall survival Trend HRs/95% CIs/*P*	
PVN		6.4/3.20-12.63/ <.001		8.21/3.80-17.54/ <.001	
pTNM		0.95/0.70-1.30/ .743		0.93/0.68-1.28/.653	
PVN		6.73/3.34-13.68/ <.001		9.84/4.51-21.63/ <.001	
AJCC		0.90/0.64-1.29/ .561		0.81/0.58-1.13/.216	
PVN		5.53/2.95-10.35/ <.001		6.54/3.30-13.01/ <.001	
JpTNM		1.12/0.80-1.56/ .498		1.33/0.93-1.88/.109	

Abbreviations: Int, intermediate; TRR, tumor recurrence rate; MR, mortality rate.
NOTE. Multivariate analyses were performed between PVN and pTNM, between PVN and AJCC, and between PVN and JpTNM, respectively.

embolus, >4 mitotic figures in a lymph node metastasis, presence of tumor necrosis in a lymph node metastasis, presence of an abundant fibrous stroma in a lymph node metastasis, and presence of fibroblasts with a conspicuous cytoplasm in the stroma in a lymph node metastasis. A score of 0 was recorded for each of the above items that were absent, and the total PVN score of the EBDCs was calculated. Patients were classified as low-, intermediate-, or high-risk according to total PVN score.

2.3. Comparison with other prognostic histologic classifications

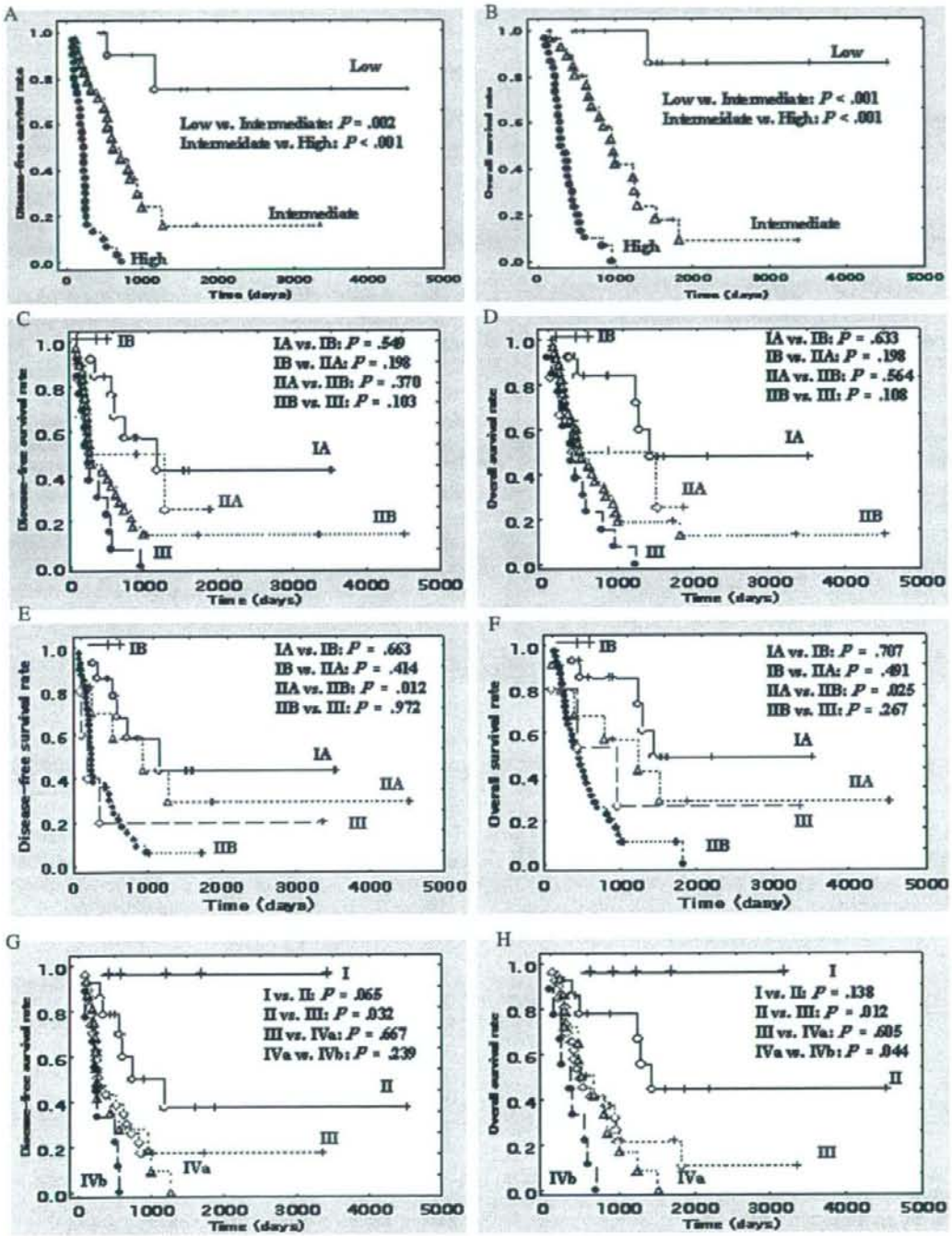
The following existing histologic classifications were compared with the PVN classification in regard to prediction of disease-free survival and overall survival: (1) pTNM [1], (2) AJCC [9], and (3) JpTNM [6]. Briefly, the JpTNM classification consists of T, N, and M categories. The T category is based on the following parameters of the primary tumor: (1) depth of invasion (carcinoma in situ, to the fibromuscular layer, to the subserosa, and to beyond the serosa) and (2) the presence or absence of direct invasion of the liver, pancreas, gallbladder, portal vein, and hepatic artery. The degree of direct invasion of the above organs was accurately determined histologically; and the tumors were classified as pT1, pT2, pT3, or pT4 depending on the combinations of parameters present in the tumor. The N category classification is based on the groups of lymph nodes involved by the tumor according to the location of the primary tumor and not on the presence or absence or number of lymph nodes involved by the tumor. The tumors were classified into the following 4 N categories; (1) pN0, no evidence of nodal metastasis; (2) pN1, tumor metastasis to group 1 lymph nodes, but not to group 2 or 3 lymph nodes; (3) pN2, tumor metastasis to group 2 lymph nodes, but not to group 3 lymph nodes; and (4) pN3, tumor metastasis to group 3 lymph nodes. The M category was assigned based on the presence or absence of distant organ metastasis, but none of the subjects of this study had distant organ metastasis at the time of the initial operation. In addition, because Hong et al recently proposed a nodal classification of EBDC [11], we compared the nodal classification of Hong et al with the PVN nodal classification (Table 4) to assess its usefulness for predicting disease-free survival and overall survival.

2.4. Statistical analysis

Survival from the date of surgery was evaluated by follow-up for a median period of 32 months as of December of 2004, during which time 51 patients experienced tumor recurrence and 48 died of their disease. Metastasis or local recurrence confirmed by computed tomography, cytology, or autopsy was considered evidence of tumor relapse; and only deaths caused by EBDC were considered for the purposes of this study.

We prospectively analyzed the predictive power of each class in the PVN classification and each stage in the pTNM,

AJCC, and JpTNM classifications for tumor recurrence or death of the patients with EBDC according to their nodal status, without knowledge of the patient outcome. We also analyzed the predictive power of each nodal class in the PVN classification and each nodal class in the nodal classification of Hong et al for tumor recurrence or death of the patients with



extrahepatic bile duct cancer as a whole, without knowledge of the outcome.

The disease-free and overall survival curves of the patients according to class in the PVN classification and stage in the pTNM, AJCC, and JpTNM classifications and in each class of the PVN nodal classification and the nodal classification of Hong et al were drawn by the Kaplan-Meier method [12]; and the log-rank test [13] was used to test for significant differences between the disease-free or overall survival curves of the patients according to class in the PVN classification and stage in the pTNM, AJCC, or JpTNM classification. Multivariate analyses were performed by the Cox proportional hazard regression model [14] to evaluate the trend values of the hazard rate (HR), 95% confidence interval (CI), and the *P* values for differences in disease-free survival or overall survival between the PVN classification and the pTNM, AJCC, and JpTNM classifications and between the PVN nodal classification and the nodal classification of Hong et al.

All analyses were performed with Statistica/Windows software (StatSoft, Tulsa, OK).

3. Results

3.1. Comparison of the PVN classification with the pTNM, AJCC, and JpTNM classifications

The rates of tumor recurrence and death for the cases as a whole increased according to the order of the risk class in the PVN classification, and each risk class in the PVN classification showed significant differences in disease-free time and overall survival time in the univariate analyses (Table 2, Fig. 2A and B). Although the rates of tumor recurrence and death tended to increase according to the order of the stages in the pTNM classification, no significant difference in disease-free or overall survival time was observed between stages; and there were no cases of tumor recurrence or death in stage IB, which is a higher stage than IA (Table 2, Fig. 2C and D). The rates of tumor recurrence and death tended to increase according to the order of the stages in the AJCC classification, and there were significant differences in disease-free and overall survival time between stages IIA and IIB. However, there were no significant differences in disease-free or overall survival time among the other stages and no cases of tumor recurrence or death in stage IB, which is a higher stage than IA; and the tumor recurrence and death rate were lower in stage III than those in stage IIB, which is a lower stage (Table 2, Fig. 2E and F). The tumor recurrence rate and death rate increased according to the order of the stages in the JpTNM classification. Significant differences in disease-free survival time and overall survival time were observed between stages II and III, and overall survival time in stage IVb was significantly shorter than that in stage IVa (Table 2, Fig. 2G and H). The multivariate analyses showed significant increases in the trend HRs for tumor recurrence and death only for the PVN classification in comparison with the other classifications (Table 2).

3.2. Comparison of the PVN classification with the pTNM, AJCC, and JpTNM classifications according to nodal status

The rates of tumor recurrence and death increased according to the order of the risk class in the PVN classification, and the univariate analyses showed significant differences in disease-free and overall survival time in each risk class in the PVN classification independent of the nodal status of the tumors (Table 3, Fig. 3A-D). Although the pTNM classification did not show significant differences in disease-free or overall survival period in patients with EBDC without nodal metastasis, the univariate analyses showed a marginally significant and a significant difference in disease-free survival time and overall survival time, respectively, in patients with EBDC with nodal metastasis (Table 3). The AJCC classification did not show any significant difference in disease-free survival time or overall survival time in patients with EBDC according to whether or not they had nodal metastasis (Table 3). Although the tumor recurrence rate and death rate of the patients with EBDC tended to increase according to the order of the stage in the JpTNM classification whether they had nodal metastasis or not, the univariate analyses showed no significant differences in disease-free survival time or overall survival time between the stages of the classification according to nodal status (Table 3). The multivariate analyses showed that only the

Fig. 2 The disease-free survival and the overall survival curves of all patients with EBDC according to the PVN, pTNM, AJCC, and JpTNM classifications. A and B, The disease-free survival time and overall survival time of each risk class decreased significantly according to the order of the risk class in the PVN classification. C and D, The disease-free survival time and overall survival time for each stage tended to decrease according to the order of the stages in the pTNM classification, but there were no significant differences in disease-free survival time or overall survival time between the stages in the classification. There were no cases of tumor recurrence or death in stage IB in the classification. E and F, Disease-free survival time and overall survival time tended to decrease according to the order of the stages in the AJCC classification; but the only significant differences observed were in disease-free survival time and overall survival time between stages IIA and IIB, and there were no cases of tumor recurrence or death in stage IB. G and H, Disease-free survival time and overall survival time in the JpTNM classification decreased according to the order of the stages in the classification, and disease-free survival time was significantly shorter in stage III than in stage II. A significantly shorter overall survival time is observed in stage II than in stage III, and in stage IVa than in stage IVb.

Table 3 Crude disease-free survival and overall survival for PVN, pTNM, AJCC, and JpTNM classifications in patients with EBDC according to nodal status

Classifications					
Patients with EBDC without nodal metastasis					
PVN					
Classes	Cases	TRR (%)	*P*	MR (%)	*P*
Low	12	2 (17)		1 (8)	
Int	12	7 (58)	.009	7 (58)	.001
High	4	4 (100)	.018	4 (100)	.032
Total	28	13		12	
pTNM					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
IA	13	6 (46)		5 (38)	
IB	3	0	.549	0	.633
IIA	6	4 (67)	.198	4 (67)	.198
IIB	3	0	.167	0	.247
III	3	3 (100)	.153	3 (100)	.153
Total	28	13		12	
AJCC					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
IA	14	6 (43)		5 (36)	
IB	2	0	.663	0	.707
IIA	11	6 (55)	.414	6 (55)	.491
III	1	1 (100)	.423	1 (100)	.626
Total	28	13		12	
JpTNM					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
I	5	0		0	
II	13	7 (54)	.065	6 (46)	.138
III	5	3 (60)	.312	3 (60)	.159
IVa	5	3 (60)	.139	3 (60)	.188
Total	28	13		12	
Multivariate analyses					
Classifications		Disease-free survival		Overall survival	
		Trend HRs/95% CIs/*P*		Trend HRs/95% CIs/*P*	
PVN		7.88/2.78-24.00/ <.001		5.41/2.12-13.89/ <.001	
pTNM		0.63/0.35-1.13/ .121		0.73/0.40-1.31/ .297	
PVN		13.33/3.01-59.12/ <.001		18.55/2.72-126.57/<.001	
AJCC		0.57/0.31-1.10/ .066		0.59/0.29-1.19/ .138	
PVN		5.07/2.18-11.74/ <.001		3.80/1.81-7.43/ <.001	
JpTNM		0.83/0.42-1.64/ .588		1.10/0.55-2.24/ .782	
Patients with EBDC with nodal metastasis					
PVN					
Classes	Cases	TRR (%)	*P*	MR (%)	*P*
Int	18	12 (67)		11 (61)	
High	26	26 (100)	.015	25 (96)	.006
Total	44	38		36	
pTNM					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
IIB	34	28 (82)		26 (76)	
III	10	10 (100)	.052	10 (100)	.029
Total	44	38		36	
AJCC					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
IIB	40	35 (88)		34 (85)	
III	4	3 (75)	.972	2 (50)	.420
Total	44	38		36	
JpTNM					
Stages	Cases	TRR (%)	*P*	MR (%)	*P*
II	1	0		0	
III	23	18 (78)	.392	17 (74)	.543
IVa	11	11 (100)	.156	10 (91)	.224
IVb	9	9 (100)	.754	9 (100)	.253
Total	44	38		36	
Multivariate analyses					
Classifications		Disease-free survival		Overall survival	
		Trend HRs/95% CIs/*P*		Trend HRs/95% CIs/*P*	
PVN		3.62/1.56-8.44/ .003		5.22/2.07-13.08/ <.001	
pTNM		1.35/0.60-3.62/ .466		1.41/0.62-3.20/ .413	
PVN		4.16/1.87-9.33/ <.001		5.68/2.36-13.76/ <.001	
AJCC		1.49/0.43-5.13/ .531		0.68/0.15-3.00/ .612	
PVN		3.63/1.60-8.28/ .002		5.41/2.20-13.35/ <.001	
JpTNM		1.24/0.84-1.84/ .277		1.45/0.98-2.14/ .074	

NOTE. Multivariate analyses were performed between PVN and pTNM, between PVN and AJCC, and between PVN and JpTNM, respectively.

PVN classification yielded a significant increase in the trend values for the HRs, 95% CI values, and *P* values in comparison with the pTNM, AJCC, and JpTNM classifications (Table 3).

3.3. Comparison of the PVN nodal classification with the nodal classification of Hong et al

The rates of tumor recurrence and death increased according to the order of the nodal category in the PVN nodal classification, and the univariate analyses showed significant differences in disease-free survival in each nodal category in the PVN nodal classification (Table 4, Fig. 4A). The PVN nodal classification showed a significant difference between N0 and N1 and a marginally significant difference between N1 and N2 (Table 4, Fig. 4B). The nodal classification of Hong et al showed significant differences in disease-free survival and overall survival between N0 and N1 in the univariate analyses, but no significant difference

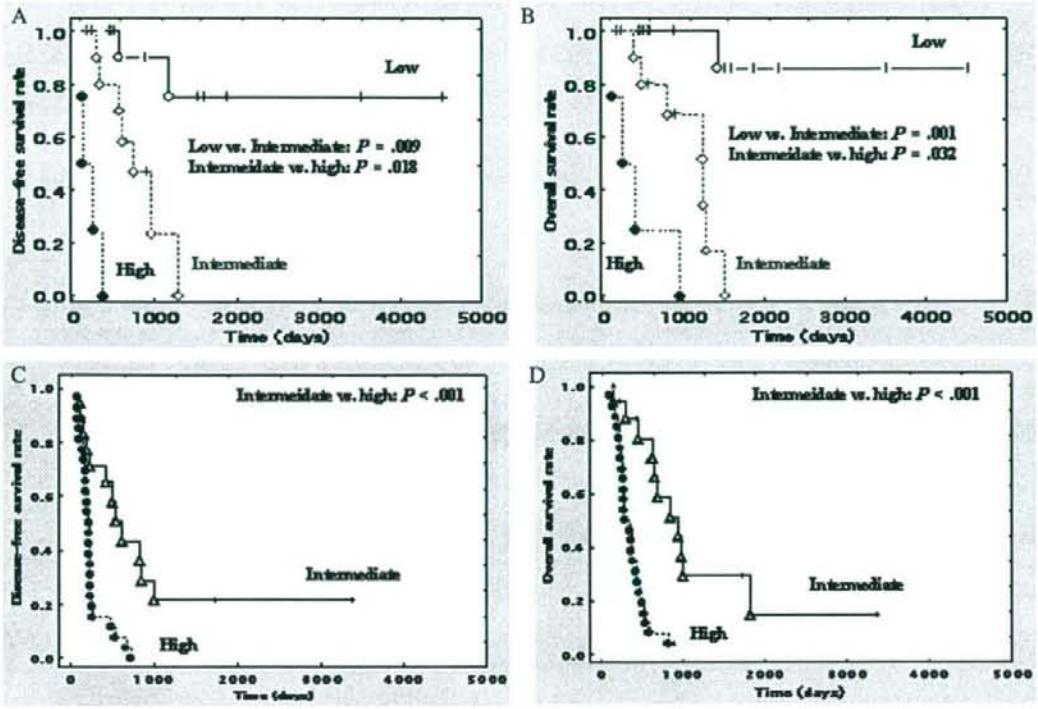


Fig. 3 Disease-free survival and overall survival curves according to the PVN classification of EBDCs according to nodal status. A and B, EBDCs without nodal metastasis. C and D, EBDCs with nodal metastasis. A to D, Disease-free survival time and overall survival time decreased according to the order of the risk class in the classification independent of nodal status.

was observed in disease-free survival or overall survival between N1 and N2 in the univariate analyses (Table 4, Fig. 4C and D). The multivariate analyses showed that the PVN nodal classification significantly increased the trend values for the HRs of disease-free survival and overall survival, but the nodal classification of Hong et al failed to significantly increase the trend values of the HRs of disease-free survival or overall survival (Table 4).

4. Discussion

The results of this study clearly demonstrated that the PVN classification is the only prognostic classification that enables classification of patients with EBDC into 3 groups according to the order of the risk in the classification with significant rates of tumor recurrence and death independent of nodal status. Because the parameters of the PVN classification were selected based on a study that accurately evaluated the histologic characteristics of primary invasive tumors, tumor cells in vessels, and tumor cells in lymph nodes [8], they are likely to be the most suitable parameters for accurately assessing the biological malignant potential of EBDCs. We therefore concluded that the PVN classification is probably the best prognostic histologic classification available for EBDC.

The comparisons with other classification systems also clearly demonstrated their drawbacks in regard to predicting the outcome of patients with EBDC. Although the JpTNM classification precisely classified the tumors according to N category based on the location of the lymph nodes involved by the tumors, it had no power to predict the outcome of patients with EBDC with lymph node metastasis. Although the N category of the pTNM classification is based on whether or not lymph nodes are involved by tumors, the results of this study showed that it was superior to the JpTNM classification for predicting the outcome of patients with EBDC with nodal metastasis. The AJCC classification also failed to accurately predict the outcome of patients with EBDC. The results of the comparison with the nodal classification of Hong et al in the present study also clearly demonstrated that the PVN nodal classification has superior predictive power for tumor recurrence and tumor death. We can therefore conclude that neither identification of the location of lymph nodes involved by tumor in the JpTNM classification nor identification of the number of lymph nodes involved by tumor in the nodal classification of Hong et al is useful for predicting the outcome of patients with

Table 4 Crude disease-free survival and overall survival of all patients with EBDC according to the PVN nodal classification and the nodal classification of Hong et al

Parameters		Score			
PVN nodal classification					
1. No. of mitotic figures in nodal metastatic tumors (in 1 high-power field)					
≤4 *vs* >4		0 *vs* 1			
2. Tumor necrosis in nodal metastatic tumors					
Absent *vs* present		0 *vs* 1			
3. Fibrosis grade of tumor stroma in nodal metastatic tumors					
None/scanty/moderately abundant *vs* abundant		0 *vs* 1			
4. Fibroblasts with a conspicuous cytoplasm in nodal metastatic tumors					
Inconspicuous *vs* conspicuous		0 *vs* 1			
		Total: 0-4			
Classes in the PVN nodal classification					
N0		No nodal metastasis			
N1		N+ and score 0-2			
N2		N+ and score 3 or 4			
Classes in the nodal classification of Hong et al					
N0		No nodal metastasis			
N1		1-4 nodal metastases			
N2		5 or more nodal metastases			
Classifications					
PVN nodal classification					
Classes	Cases	TRR (%)	*P*	MR (%)	*P*
N0	28	13 (46)		12 (43)	
N1	37	31 (84)	<.001	29 (78)	<.001
N2	7	7 (100)	.049	7 (100)	.051
Total	72	51		48	
Nodal classification of Hong et al					
Classes	Cases	TRR (%)	*P*	MR (%)	*P*
N0	28	13 (46)		12 (43)	
N1	33	27 (82)	<.001	25 (76)	.001
N2	11	11 (100)	.104	11 (100)	.068
Total	72	51		48	
Multivariate analyses					
Classifications		Disease-free survival Trend HRs/95% CIs/*P*		Overall survival Trend HRs/95% CIs/*P*	
PVN nodal classification		2.25/1.15-4.38/.016		4.46/1.05-3.96/.035	
Nodal classification of Hong et al		1.41/0.80-2.48/.241		1.53/0.86-2.71/.150	

NOTE. Multivariate analyses were performed between the PVN nodal classification and the nodal classification of Hong et al.

EBDC with nodal metastasis, and that assessment of the characteristics of the tumor cells and tumor stromal cells in nodal metastatic tumors is probably the best way to accurately evaluate the true malignant potential of EBDCs in patients with nodal metastasis.

The pTNM, AJCC, and JpTNM classifications of EBDC assess the degree of invasion of surrounding organs, for example, pancreas, liver, gallbladder, and main portal vein, by the primary tumor; but the results of the univariate analyses according to nodal status showed that they failed to significantly predict the outcome of patients with EBDC. We had already demonstrated that the degree of invasion of surrounding organs by the primary tumor is of no prognostic value for predicting the outcome of patients with EBDC [8]; and Hong et al also showed that the degree of invasion of surrounding organs by the primary tumors loses its prognostic power when analyzed after adjustment for depth of invasion by the primary tumor, nodal status, or other prognostic parameters [10]. Thus, assessment of the degree of invasion of surrounding organs by the primary tumor can be concluded to be of no benefit for predicting the outcome of patients with EBDC. In the PVN classification, the primary tumor is assessed only according to the depth of invasion of the extrahepatic bile duct by the primary tumor. It can therefore be concluded that pathologists should assess the histologic characteristics of tumor cells and tumor stromal cells in lymph vessel tumor emboli or blood vessel tumor emboli instead of the degree of invasion of organs surrounding the extrahepatic bile duct by the primary tumor. Based on these findings, the histologic characteristics of the T and N categories of the pTNM, the AJCC, or the JpTNM classification should be improved by including some histologic factors composing the PVN classification because these classifications are the prognostic classifications of EBDC that are being used worldwide.

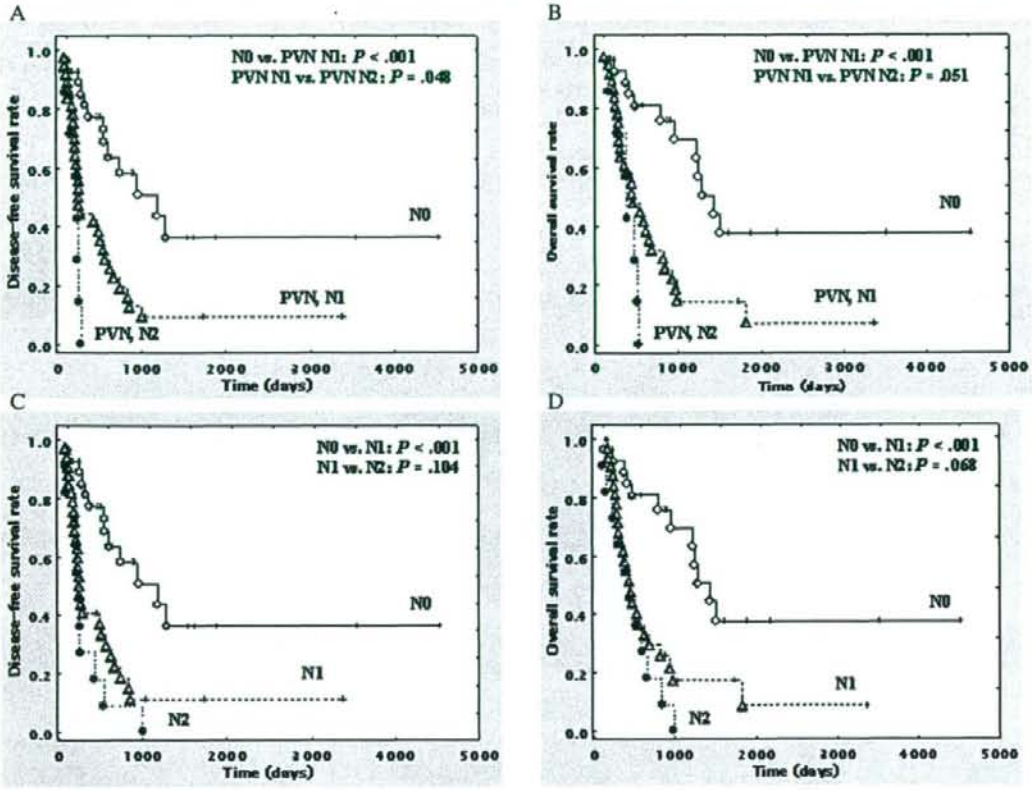


Fig. 4 Disease-free survival and overall survival curves according to the PVN nodal classification and the nodal classification of Hong et al of all patients with EBDC. A and B, Disease-free survival time and overall survival time in the risk categories in the PVN nodal classification decreased according to the order of the risk categories in the classification. C and D, N1 in the nodal classification of Hong et al was associated with significantly shorter disease-free survival time and overall survival time than N0, but there was no significant difference in disease-free survival time or overall survival time between N1 and N2 in the classification.

In conclusion, the results of this study clearly demonstrated that the PVN classification is the most accurate histologic classification for predicting the outcome of patients with EBDC. However, because the methodology for making classifications by the PVN system may be more complex than that by the existing classification systems, it may be difficult to apply the PVN classification in ordinary diagnostic settings; and the degree of interobserver variability in assessments of the factors comprising the PVN classification should be examined in the near future. Advances in technology in the field of medical research are being made daily, and they have made many new important findings possible in cancer research. The results in the field of histologic examination of tumors have led to the new concept that assessing not only the histologic features of the primary tumor but of tumor cells and tumor stromal cells in vessels or lymph nodes is most likely to enable accurate determination of the malignant potential of all kinds of tumors. Pathologists should therefore make an effort to assess the true malignant potential of EBDCs by using the criteria of the PVN classification.

References

[1] Sobin LH, Wittekind CH, editors. TNM classification of malignant tumors. 6th ed. New York (NY): Wiley-Liss; 2002. p. 87-9.

[2] Backes BG, Hauptmann S, Bocking A. Carcinoma of the extrahepatic biliary system: correlation of clinical, pathological, histological and DNA-cytometric parameters with prognosis. Anticancer Res 2000;20: 1163-8.

[3] Klempnauer J, Ridder GJ, von Wasielewski R, et al. Resectional surgery of hilar cholangiocarcinoma: a multivariate analysis of prognostic factors. J Clin Oncol 1997;15:947-54.

[4] Nishida T, Nakao K, Hamaji M, et al. Prognostic significance of proliferative cell nuclear antigen in carcinoma of the extrahepatic bile duct. World J Surg 1997;6:634-9.

[5] Zerbi A, Balzano G, Leone BE, et al. Clinical presentation, diagnosis and survival of resected distal bile duct cancer. Dig Surg 1998;15: 410-6.

[6] Nakagawa T, editor. Japanese Society of Biliary Surgery. Classification of biliary tract carcinoma. 2nd ed. Tokyo: Kanehara & Co., Ltd; 2004. p. 11-32.
[7] Hasebe T, Sasaki S, Imoto S, et al. Primary tumor-vessel tumor-nodal tumor classification for patients with invasive ductal carcinoma of the breast. Br J Cancer 2005;92:847-56.
[8] Hasebe T, Konishi M, Iwasaki M, et al. Histological characteristics of tumor cells and stromal cells in vessels and lymph nodes are important prognostic parameter of extrahepatic bile duct carcinoma: a prospective study. Hum Pathol 2005;36: 655-64.
[9] Fleming ID, Cooper JS, Hensen DE, et al, editors. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag; 2002. p. 163-9.
[10] Hong SM, Kim MJ, Pi DY, et al. Analysis of extrahepatic bile duct carcinomas according to the new American Joint Committee on Cancer staging system focused on tumor classification problems in 222 patients. Cancer 2005;104:802-10.
[11] Hong SM, Cho HJ, Lee OJ, et al. The number of metastatic lymph nodes in extrahepatic bile duct carcinoma as a prognostic factor. Am J Surg Pathol 2005;29:1177-83.
[12] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
[13] Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patients. II. Analysis and examples. Br J Cancer 1977;35:1-39.
[14] Cox DR. Regression models and life-tables. J R Stat Soc 1972;34: 187-220.

日本臨牀　66巻 増刊号5（2008年7月28日発行）別刷

胃　　癌

—基礎・臨床研究のアップデート—

XII. 臨床的事項—診断・治療の最新動向を中心に—

スキルス胃癌

木下　平

XII. 臨床的事項—診断・治療の最新動向を中心に—

スキルス胃癌

Scirrhous gastric cancer

木下 平

Key words：スキルス胃癌，手術，補助療法

はじめに

スキルス胃癌は胃癌の特殊系であり，びまん浸潤性胃癌，linitis plastica(LP)型胃癌，Borrmann 4型胃癌などと同義語として使われており，極めて予後不良な悪性度の高い病型として知られている．

胃体部に発生するものと幽門部に発生するものがあり，前者は胃底腺領域に発生し巨大皺襞を呈したり，胃壁全体が硬化性に肥厚し，leather bottle状を呈するようないわゆるLP型と呼ばれる典型的なスキルス胃癌である．後者は幽門腺領域に発生し胃体部方向に進展する幽門型と呼ばれている．発生部位は異なるが，どちらも癌が胃壁内をびまん性に浸潤し，高度の胃壁の線維性肥厚をきたす特徴をもっている．前述した2つのタイプ以外にも，Borrmann 3型の進行癌で隆起陥凹部分に比して周辺に明らかに広範なスキルス進展を伴うものもスキルス胃癌に分類されることが多い[1,2]．

スキルス胃癌の早期像はいずれのタイプでもひだ集中を伴わない平坦，陥凹型の早期癌と考えられているが[1,2]，現実にはその中間時期と考えられる症例に遭遇する機会は極めて少ない．

スキルス胃癌は発見されたときには既に胃に広範に進展し，高頻度に腹膜播種を伴っているため切除不能と判定される場合が多いのが現状である．

本稿ではスキルス胃癌に対する臨床的な取り組みを歴史的な流れとともに考察する．

1. スキルス胃癌の頻度

集計する母集団やスキルス胃癌の定義などの差があるため，全体の胃癌に占めるその頻度には幅がある．検診センター全体での発見頻度は5.3%，進行癌中では14.7%との報告がある[1]．その他の外科系施設からの報告でも進行胃癌に占めるスキルス胃癌の頻度は10-20%の報告が多い[2,3]．特にLP型に絞ってみると，女性に多く，50歳以下の若年層に多い傾向がある[1]．

2. 化学療法

スキルス胃癌に限定した化学療法のまとまった治療成績または臨床試験の成績は，medical oncologyの分野ではほとんど皆無といっても過言ではない．胃癌全体に占める頻度の問題を考えるとやむを得ないと思われる．しかし，治療の個別化という意味では今後は極めて重要な問題となってくると思われる．これまで古くはMMC，5Fuに始まり，低分化腺癌の多いスキルス胃癌の化学療法はMTX+5Fu，FAMTX，FPなどの多剤併用療法が選択されてきたが，目立った効果は得られなかった．しかしS-1の登場以来，胃癌全体のmedical oncologyの分野

Taira Kinoshita: Department of Upper Abdominal Surgical Oncology, National Cancer Center Hospital East 国立がんセンター東病院 上腹部外科

0047-1852/08/¥40/頁/JCLS

でも最近になり次々とRCTによる日本発のエビデンスが出てきている．2007年ASCOで報告されたJCOG9912ではS-1の5Fuに対する非劣性が証明され，非劣性が証明できなかったCPT+CDDPを考慮し，S-1が切除不能，再発胃癌の標準治療と考えられる結果となった．更に同様に2007年のASCOで報告されたSPIRIT trialでS-1とS-1+CDDPが比較された結果，OS，PFS，responseともに有意にS-1+CDDPが勝りfirst lineとしての標準治療の地位を得る結果となった．CF，ECF，TCF，XPなどが主流の諸外国と一線を画し，現時点では世界のglobal standardとはなりえないが，S-1 basedの化学療法が日本においては確実なstandardとなった．スキルス胃癌に関しても例に漏れず同様な歴史的変遷で治療が行われてきた．胃癌化学療法の動向としては現在S-1との併用療法の候補としてのtaxane系の薬剤，今後oxaliplatin，capecitabin，更には分子標的薬などが臨床試験の有望な薬剤としての候補になっており，国際共同治験を含め様々な臨床試験が行われ，あるいは行われる予定である．しかし，これらの試験はスキルス胃癌のみを対象にしておらず，後層別されたスキルス胃癌に対する効果からその有効性を判断せざるを得ないのが現状である．

3. 外科治療

治療成績の極めて不良なスキルス胃癌に対する外科手術での対応は，あくまで肉眼的に治癒切除可能な症例に限定される．有効な化学療法が出現してきた最近の論文では，特に姑息切除はすべきでないという意見も多くみられるようになってきた[4,5]．

胃癌では腹腔内洗浄細胞診が肉眼的に検知不可能な腹腔内の遊離癌細胞の存在を知る有用な手段であり，腹膜播種を伴わない洗浄細胞診陽性例(CY1)の予後は腹膜播種症例と同等であるため，胃癌取扱い規約第13版からCY1は非治癒切除因子と規定された[6]．腹膜播種が高頻度に起こるスキルス胃癌では洗浄細胞診は重要な検査となっている．外科切除に先駆けて行う主に転移診断である画像診断の進歩には目覚ましいものがあるが，依然として腹膜播種診断は困難である．CT，超音波検査での腹水の証明は強く腹膜播種を疑う所見であるが，細胞診で癌を証明できなければ確診に至らない．注腸透視で認められる大腸の収束像もかなり進行した腹膜播種の所見であり，開腹して初めて腹膜播種の診断を得ることが極めて高率にあるのがスキルス胃癌の特徴でもあった．しかし最近では，診断的腹腔鏡検査が多くの施設で行われるようになり，かなり正確な診断が可能となってきている[7]．

びまん性に胃壁を広範に浸潤するスキルス胃癌では，ほとんどの症例に胃全摘が行われる．これが唯一特異的な術式といえるものかもしれない．

リンパ節郭清の拡大を含めスキルス胃癌に特異的な手術術式はないが，スキルス胃癌の進展を意識した拡大手術法として左上腹部内臓全摘術がある．この術式はスキルス胃癌の周辺臓器への進展を意識して胃全摘のみならず，膵体尾部，脾，横行結腸，胆嚢，副腎を，胃を包むように一塊として切除する術式である．この術式に更に後腹膜進展に対する対策，リンパ節郭清を徹底させるため腹腔動脈を根部で切離するAppleby手術を併用する究極の拡大手術も考案された[8]．しかしその効果は限定的にしか認められず，最近ではほとんど行われることはなくなった．

外科の単独治療では限界があることは明白であり，多くの施設で補助化学療法が試行されてきた．しかしスキルス，非スキルス胃癌にかかわらず補助化学療法の有効性が証明されたのは最近になってからであり，術後にどんなに強力な化学療法を付加しても治療成績の向上は過去には得られなかったといっても過言ではない．この改善されない治療成績を打破するために術前化学療法に期待をかける施設もあり，様々な術前化学療法が行われたが，いずれの報告も少数例のpilot study規模の報告であり[9-12]，S-1が登場するまでその治療成績の改善は得られなかった．次項でその変遷につき詳述する．

4. 補助療法の変遷

前述したように有効な化学療法の出現により，スキルス胃癌の外科治療体系も変遷しつつある．前項でも述べたように補助化学療法に関してはUFT，S-1のRCTで初めて有効性のエビデンスが得られているが，UFTのNSAS-GCの対象群は早期癌を除くT2，n1-2，S-1のACTS-GCではやはり早期癌を除くStage II-IIIを対象とした試験であり，治癒切除されたスキルス胃癌が対象に入る可能性は極めてまれである．したがって，この2つの臨床試験のエビデンスがそのままスキルス胃癌のエビデンスとはなりえないことに注意しなくてはならない．しかし，S-1 basedの化学療法がスキルス胃癌術後の補助療法としてのcommunity standardとなっている状況は否めない．

術前化学療法に関しては前述したごとく様々なレジメンがpilotで行われてきたが，最初に臨床試験の体裁を整え行われたのが国立がんセンター東病院で行われたFAMTXによる第2相試験である．FAMTXがスキルス胃癌に対しても30%のPR rateがあることに注目して行われたが，毒性が強く(grade 3-4の血液毒性が70%に出現)，奏効率15%，切除標本の組織学的効果も全例grade 0-1bと悪く，中間解析の時点において20例の生存解析でhistorical controlに対し改善がみられず，中止となった[13]．その後S-1が登場し，やはり国立がんセンター東病院より連続する5例のS-1単剤による2コースの術前化学療法のpilot studyの結果が報告された．副作用もmild(grade 3-4なし)で，5例中3例にPRが得られ，3例の治癒切除例は2-3年無再発生存中と生存期間の延長も期待される報告であった[14]．この5症例中3例の治癒切除例は術後8年，7年半現在生存中で2例は無再発，1例は5年経過した時点で卵巣腫瘍の切除を行った結果，組織でKrukenberg tumorと判明し，その後S-1を1年内服，8年後の現在無再発生存中である．

これを受けJCOGでS-1単剤による2コースの術前化学療法の第2相試験が計画され行われた．55例が集積され，副作用による化学療法の中止例はなく，手術も安全に行われた．46例の切除標本の組織学的な効果判定で11例(23.9%)にgrade 2が認められ，FAMTXと比較して明らかな効果を認めた．しかし2年のfollow up終了後の生存解析で，生存曲線はhistorical controlより良好であったが，2年生存率は59%で，期待された20%の上乗せ効果の2年生存率60%にわずかに届かず，安全に施行でき有効ではあるが当初期待した目標には届かなかったという結論になった．

同時期に進行していた大型3型，スキルス胃癌に対するS-1+CDDPの第2相試験(JCOG 0210)の結果，奏効率，切除例の組織学的効果がS-1単剤に比して明らかに勝っており，生存解析でも良好な成績が得られたため，予定されていた大型3型，スキルス胃癌に対する術前化学療法の意義を問う第3相試験(JCOG0405)の試験アームの化学療法はS-1+CDDPということになり，現在既にスタートしている．ACTS-GCのエビデンス以来，多くのプロトコール改訂がなされ，術後の補助化学療法としてS-1の1年間の内服が追加された．JCOG0405も両アームに補助化学療法が追加されている．術前化学療法の有用性のエビデンスはこの試験の結果を待つ必要がある．

スキルス胃癌に特化したものではないが，このほかにもS-1+taxane系の薬剤，分子標的薬を含む新薬の臨床試験が行われており，期待されている．

以上をまとめると，スキルス胃癌に関しては現在S-1+CDDPによる術前化学療法に期待がかかっており(JCOG0405の結果次第であるが)，切除不能例に関してもS-1+CDDPがfirst lineとなっている．補助化学療法に関しても術後の安全性が臨床試験で確認されているのはS-1単剤のみであるため，現時点ではS-1単剤がcommunity standardと考えられる．JCOGでは次の補助化学療法の試験アームの候補としてのS-1+CDDPの術後投与の安全性を確認する第2相試験(JCOG00065)を始めている．

表1 術前に化学療法を行った症例の概要

	(治癒切除例：%)
down stage	**12例(3：25%)**
FAMTX	5例(0：0%)
S-1	4例(2：50%)
S-1+CDDP	2例(1：50%)
CPT+MMC	1例(0：0%)
計画的術前化学療法	**49例(38：78%)**
FAMTX	20例(13：65%)
S-1	11例(7：64%)
S-1+CDDP	18例(15：83%*)

*Po CY1が2例，p PM(+)が1例.

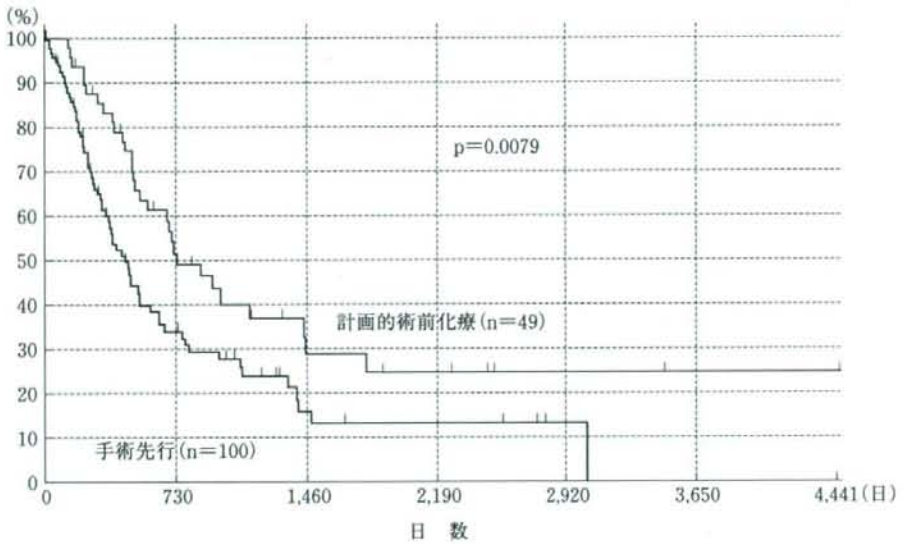


図1 計画的術前化学療法例，手術先行例の生存曲線

5. 国立がんセンター東病院での治療成績

スキルス胃癌に対する取り組みは前述したごとくその頻度が低いことから，臨床試験により独立したエビデンスを作ることは困難である．数少ない独立したエビデンスになりうるJCOG studyの結果を待つ必要があるが，参考までに当院での治療成績を紹介する．

開院以来2006年7月までに当院で経験したスキルス胃癌開腹例は161症例あり，手術先行が100例，化学療法先行が61例で，化学療法先行例の内訳は計画的術前化学療法(49例)，切除不能であったが化学療法によりdown stageが得られ手術となった症例が12例であった．

表1に術前に化学療法が入った症例の内容を示す．

図1に手術先行例と計画的化学療法例の生存曲線を提示する．手術先行例に対し計画的術前化学療法施行例の5年生存は有意に良好であった(25% vs 13%，p=0.0079)．

計画的化学療法例をレジメン別にみると，S-1 based(S-1単剤：11例，S-1+CDDP：18例)では5年生存率は40%と，FAMTX群(20例)の10%に比し有意に(p=0.0043)良好であった(**図2**)．

S-1 basedの術前化学療法を始めた初期には

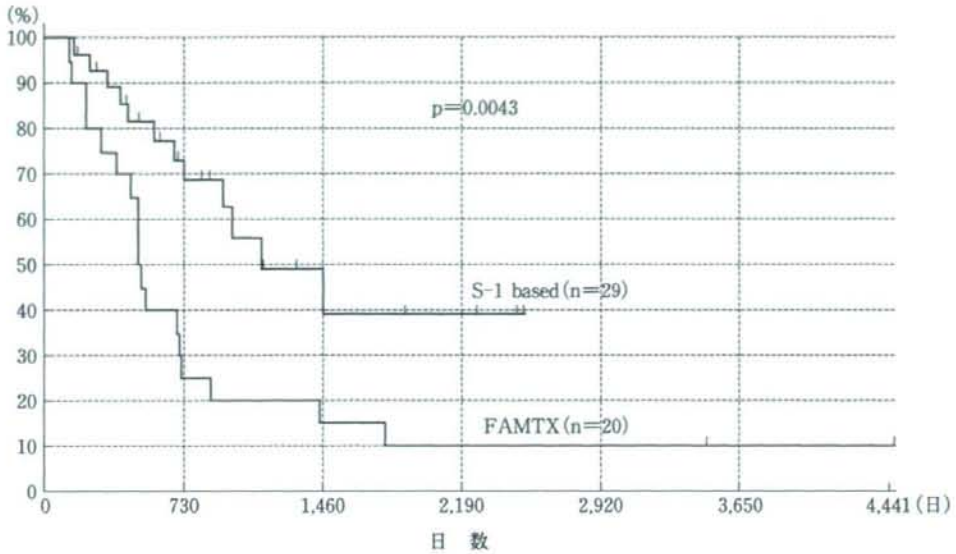


図2 S-1 basedとFAMTX症例の生存曲線

術後補助化学療法は行っていなかったが，ACTS-GCのエビデンスの発表以降は全例にS-1による補助化学療法を施行している．

11例のS-1 basedの術前化学療法の5年生存例は4例で，前述したKrukenberg再発で補助化学療法を行った1例を除く3例はS-1単剤術前化学療法のみの症例であった．S-1+CDDP症例はS-1単剤に比しfollow up期間がまだ短いため5年以上の長期生存例はないが，いずれにせよS-1 based neoadjuvant chemotherapyはスキルス胃癌にも有効であると考えられる．

以上スキルス胃癌に対する治療の現状を臨床的な側面から述べた．

■文 献

1) 西澤 護ほか：診断医からみたスキルス胃癌の早期像．臨床外科 48: 1505-1511, 1993.
2) 下田忠和ほか：びまん浸潤性(スキルス)胃癌の病理学的特徴—特にその初期像について．臨床外科 48: 1513-1521, 1993.
3) 太田恵一朗ほか：びまん浸潤型胃癌の浸潤と転移—他臓器浸潤例とリンパ行性浸潤例の治療について．臨床外科 48: 1523-1528, 1993.
4) Kunisaki C, et al: Therapeutic strategy for scirrhous type gastric cancer. Hepatogastroenterology 52: 314-318, 2005.
5) Yoshikawa T, et al: Should scirrhous gastric carcinoma be treated surgically? Clinical experiences with 233 cases and a retrospective analysis of prognosticators. Hepatogastroenterology 48: 1509-1512, 2001.
6) 日本胃癌学会(編)：胃癌取扱い規約，第13版，金原出版，1999.
7) Shiraishi N, et al: Laparoscopy in the management of scirrhous gastric cancer. Gastric Cancer 2: 109-114, 1999.
8) Furukawa H, et al: Extended surgery—left upper abdominal exenteration plus Appleby's method—for type 4 gastric carcinoma. Ann Surg Oncol 4: 209-214, 1997.
9) Mai M, et al: Study on neoadjuvant chemotherapy of Borrmann 4 type carcinoma of the stomach and its clinical significance. Nippon Gan Chiryo Gakkai Shi (J Jpn Soc Cancer Ther) 25: 586-597, 1990.

10) Maeda O, et al: Scirrhous cancer of the stomach which survived for more than 5 years after neoadjuvant chemotherapy with UFT(uracil and tegafur) and cisplatin. Intern Med **39**: 239–244, 2000.
11) Eriguchi M, et al: Pilot study for preoperative administration of l-OHP to patients with advanced scirrhous type gastric cancer. Biomed Pharmacother **51**: 217–220, 1997.
12) Suga S, et al: Neoadjuvant chemotherapy in scirrhous cancer of the stomach using uracil, tegafur and cisplatin. Intern Med **35**: 930–936, 1996.
13) Takahashi S, et al: Phase II study of sequential high-dose methotrexate and fluorouracil combined with doxorubicin as a neoadjuvant chemotherapy for scirrhous gastric cancer. Gastric Cancer **4**: 192–197, 2001.
14) Kinoshita T, et al: Neoadjuvant chemotherapy with S-1 for scirrhous gastric cancer—A pilot study. Gastric Cancer **6**: 40–44, 2003.

早期胃癌における術前 MDCT の有用性の検討

国立がんセンター東病院上腹部外科
信岡大輔　後藤田直人　小西大
中郡聡夫　高橋進一郎　木下平

DIAGNOSTIC PERFORMANCE OF MDCT FOR EARLY GASTRIC CANCER

Daisuke NOBUOKA, Naoto GOTOHDA, Masaru KONISHI,
Toshio NAKAGOHRI, Shinichiro TAKAHASHI and Taira KINOSHITA
Department of Surgery, National Cancer Center Hospital East

日本臨床外科学会雑誌　第69巻　6号　別刷
(平成20年6月25日発行)

日臨外会誌　69（6），1303—1307，2008

原　著

早期胃癌における術前 MDCT の有用性の検討

国立がんセンター東病院上腹部外科
信岡大輔　後藤田直人　小西　大
中郡聡夫　高橋進一郎　木下　平

目的：早期胃癌の術前検査における MDCT の有用性を評価し，必須か，あるいは省略可能かにつき検討する．対象および方法：2006年の1年間に当院で行った胃癌手術のうち術前診断 T1の144例を対象とし，術前検査所見を手術所見および病理所見と比較検討した．結果：リンパ節転移診断の感度は7％，特異度は97％，正診率は87％であった．術前 MDCT にて検出された他疾患には胆嚢結石・肝血管腫・肝嚢胞・腎嚢胞等があるも，胆嚢疾患以外は術式決定に影響を及ぼさず，またその殆どが超音波検査で検出可能であった．考察：MDCT は早期胃癌では腫瘍描出能が悪いうえリンパ節転移診断の正診率も低く，術前 staging としての有用性は低いと考えられた．MDCT の結果で手術操作の変更・追加を要した事例は認められなかった．結論：早期胃癌の術前検査において MDCT の有用性は低く超音波検査で代用できる可能性が示唆された．

索引用語：早期胃癌，術前検査，multidetector-row CT，リンパ節転移，超音波検査

緒　言

今日の胃癌治療はガイドラインにより病期ごとに適応となる治療法が明示されている[1]が，治療法選択のためには術前に進行度を正確に診断することが不可欠である．胃癌の術前検査としては，上部消化管内視鏡と生検，上部消化管造影，腹部 CT 検査，腹部超音波検査，超音波内視鏡などが日常的に行われている．

近年の画像診断の進歩は目覚ましく，なかでも multidetector-row CT（以下，MDCT）の登場とワークステーションの発達はその画像解析能において従来の CT 検査をはるかに凌駕した[2][3]．その結果 MDCT は現在，胃癌の術前検査として staging と他病変検索の目的で広く用いられている．MDCT はその優れた空間分解能により，進行胃癌の周囲への進展，リンパ節転移，肝転移，腹膜転移の描出に有用とされる[4]~[6]．しかし，一方で早期胃癌における原発巣の深達度およびリンパ節転移診断などについては，満足すべき報告はない[7]~[10]．また MDCT はその検査の低侵襲性・簡便性と得られる情報量の多さから当院では撮影件数が増加の一途を辿っており，現在その飽和した CT 検査件数から内科系外科系を問わず，必要性の見直しが迫られている．こうした実情は全国の基幹施設など患者集中のみられる多くの施設で抱える問題ではないかと推測する．

そこでわれわれは，今回早期胃癌の術前検査における MDCT の有用性を評価し，MDCT は必須か，あるいは省略可能かどうかにつき検討を行った．

対象および方法

2006年1月より12月までの1年間に当院で行った胃癌手術280例のうち，術前内視鏡および上部消化管造影にて cT1と診断された144例を対象とし（図1），術前検査所見を手術所見および切除標本の病理組織学的所見と比較して MDCT の有用性につき検討した．

MDCT は4列もしくは16列検出器 CT 装置を使用し，画像再構成は5 mm スライス厚を基本とした．造影剤アレルギーなどの特別な理由がない限り非イオン性ヨード系造影剤を使用し，造影前と門脈相（造影剤注入後70秒）とで撮影した．

進行度診断は第13版胃癌取扱い規約[11]に従った．術前リンパ節転移診断に関しては MDCT で短軸径10 mm 以上を基本とし，そこに形状・造影効果の所見を加えて総合的に判定した．全症例の術前診断は放射線

2008年2月20日受付　2008年4月8日採用
〈所属施設住所〉
〒277-8577　柏市柏の葉6—5—1