*Back ground and clinical symptoms*

All AIP patients were male and had no other autoimmune-related disorders or history of alcohol abuse. Their age range was 51–68 years, with a mean of 60.9 years. Abdominal symptoms were present in 4 cases; however, they were mild, with epigastric discomfort rather than pain. The other 3 patients had no abdominal symptoms (Table I).

A total of 5 patients had mass lesions in the head of the pancreas. Four patients presented with obstructive jaundice, but fluctuation of jaundice was not observed in any of the patients. The other patient with a pancreatic head mass did not show obstructive jaundice, although the tumor was large at 30 mm in diameter.

*Laboratory data*

Serum level of IgG4 was measured in only 2 patients with AIP, and was above the normal limit (normal range: 0–135 mg/dl [13]) in both of them. Regarding tumor markers, carcinoembryonic antigen (CEA) was within normal limits in all patients; however, carbohydrate antigen (CA) 19-9 was raised in 2 patients. Autoantibodies were not evaluated (Table I).

*Dynamic CT images*

Every patient showed a localized pancreatic lesion, and to some extent delayed enhancement in dynamic CT studies. The degree of mass formation varied from mild swelling of the parenchyma to a distinct tumor-like lesion. A capsule-like rim was identified in only one patient. Neither a cystic component nor calcification was detected (Table I, Figures 1 and 2).

*Main pancreatic duct*

Apart from the case involving the uncinate process with a normal main pancreatic duct (MPD), a duct in the area of the mass lesion was observed in the other 6 patients. Four patients who underwent endoscopic retrograde pancreatography (ERP) showed smooth or irregular narrowing of the MPD, whereas the two patients who recently received magnetic resonance pancreatography (MRP) demonstrated obstruction of the MPD in accordance with the tumor (Table II, Figures 3 and 4).

Post-stenotic dilatation of the MPD was observed in all patients with the exception of two; one of these patients had a tumor in the uncinate process and therefore showed normal pancreatic duct features, and the other had a mass located in the body-tail of the pancreas, so the post-stenotic status was not evaluated. However, post-stenotic dilatation was mild and the MPD had a maximum diameter of less than 5 mm in all patients.

*Common bile duct*

Stricture of the lower common bile duct was detected on endoscopic retrograde cholangiography (ERC) or magnetic resonance cholangiography (MRC) in all 5 patients with a pancreatic head lesion, including one patient without obstructive jaundice.

*Findings of mass-forming pancreatitis*

Clinical and radiological findings of chronic pancreatitis not otherwise specified were also reviewed (Table III). The mean age was 49.6 years and younger than that for patients with focal-type AIP.

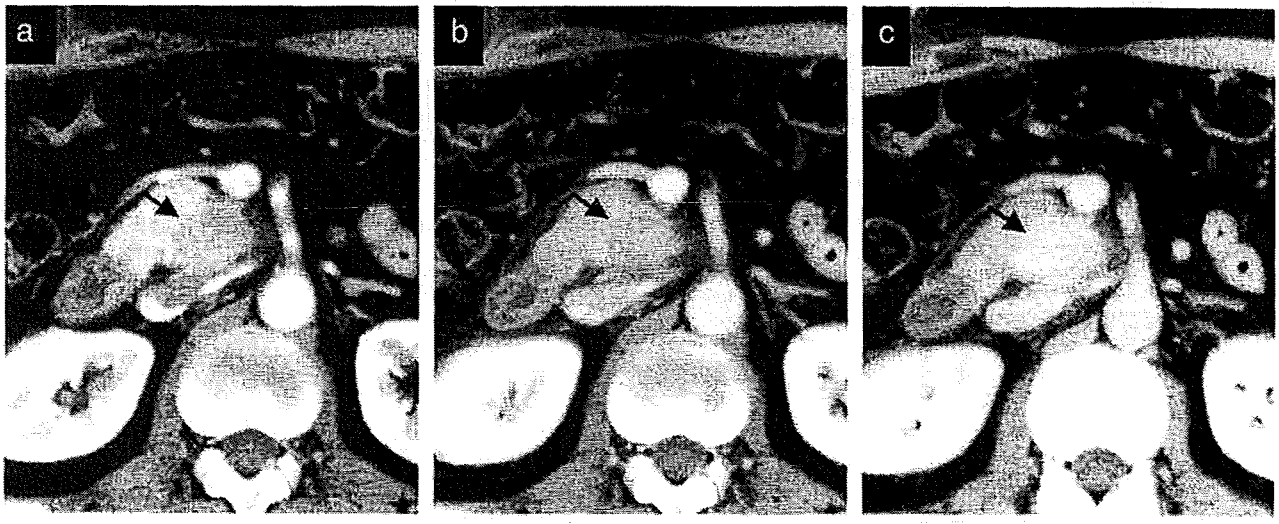


Figure 1. Dynamic computed tomography (CT) in case 3 shows a distinct mass lesion in the head of the pancreas with delayed enhancement (*arrows*). (a) Arterial phase, (b) portal phase, (c) delayed phase.

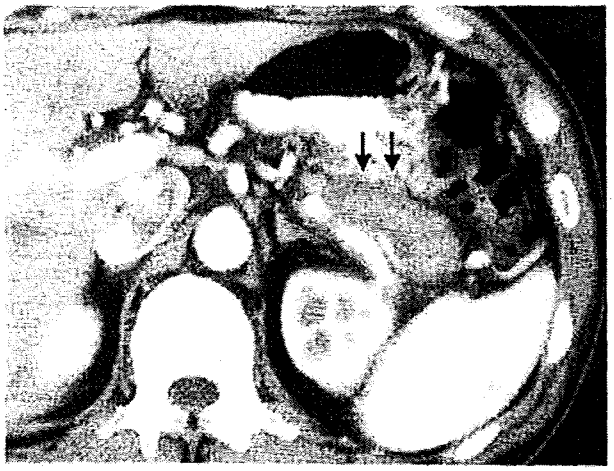

Figure 2. Arterial phase, contrast-enhanced computed tomography (CT) in case 4 shows a mass-like lesion in the body to tail of the pancreas, with a low-attenuated capsule-like rim (*arrows*).

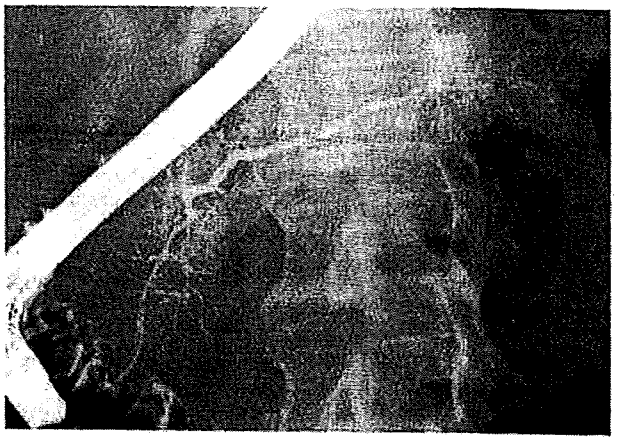

Figure 3. Endoscopic retrograde pancreatography (ERP) in case 6 shows segmental smooth narrowing of the main pancreatic duct (MPD) in the pancreatic head, with mild upstream dilatation (maximum diameter is 4 mm).

Three patients had a history of alcohol abuse. Although 7 out of 8 patients had lesions in the head of the pancreas, obstructive jaundice was observed in only 2 patients.

On dynamic CT examination, 5 patients showed delayed enhancement to some extent. Cystic lesions and calcification in the tumor, which were not observed in focal-type AIP, were detected in 3 patients and 1 patient, respectively. MPD stenosis on MRP was detected in 2 patients; at ERP, 4 out of 6 patients showed narrowing of the MPD, whereas the other 2 patients had normal MPD features.

## Discussion

AIP is a unique entity of chronic pancreatitis, with an autoimmune etiological mechanism [1,14,15]. It is also known as lymphoplasmacytic sclerosing pancreatitis (LPSP) based on its characteristic pathological findings [9]. Clinically, obstructive jaundice is considered a major presenting symptom [16].

AIP usually affects the whole pancreas; however, a focal type of AIP, which affects a localized area of the pancreas and often exhibits mass formation, has been reported [2–7]. In fact, the diagnostic criteria for AIP proposed by the Japan Pancreas Society [17] were revised in 2006, and the description of the length of the affected pancreatic duct, which was previously defined as more than 1/3 the length of the entire pancreas, was abolished. If we consider AIP as starting as a local form that progresses to diffuse swelling of the pancreas [18], focal-type AIP can be regarded as part of the same clinical spectrum as the diffuse type of AIP. Whether the distribution is diffuse or focal merely reflects the stage or the extent of the disease [8].

This focal type of AIP has recently been recognized; therefore, there might be many cases of this clinical entity buried in pancreatic specimens that were resected for suspected pancreatic carcinoma and were diagnosed as mass-forming chronic pancreatitis in the past.

In the present study, out of 15 patients with chronic pancreatitis who underwent surgical exploration,

Table II. Radiological findings of MPD on MRP or ERP.

| | | MRP findings | | ERP findings | |
|---|---|---|---|---|---|
| Case | Location | MPD | Post-stenotic dilatation | MPD | Post-stenotic dilatation |
| 1 | Body, tail | Stenosis | 3 mm | | |
| 2 | Head, body | Stenosis | 4 mm | | |
| 3 | Head (Uncus) | Normal | – | | |
| 4 | Body–tail | | | Smooth narrowing | Not evaluated |
| 5 | Head | | | Irregular narrowing | 4 mm |
| 6 | Head | | | Smooth narrowing | 4 mm |
| 7 | Head | | | Irregular narrowing | 5 mm |

Abbreviations: MPD = main pancreatic duct; MRP = magnetic resonance pancreatography; ERP = endoscopic retrograde pancreatography.

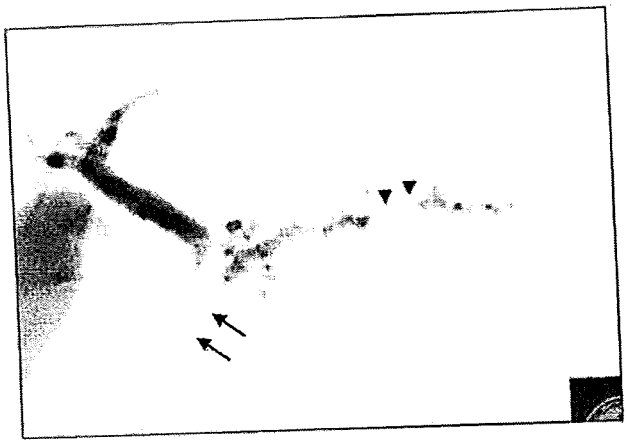

Figure 4. Magnetic resonance pancreatography (MRP) in case 2 shows segmental obstructions of the main pancreatic duct in the area of the double tumors and mild post-stenotic dilatation. (*arrows*: head lesion; *arrow heads*: body lesion).

7 were shown to have AIP and the other 8 patients were diagnosed as having mass-forming pancreatitis not otherwise specified. The pathologic diagnosis of AIP was easily made based on characteristic findings such as dense periductal lymphoplasmacytic inflammation, parenchymal fibrosis, and obliterative venulitis on hematoxylin & eosin staining. With regard to immunohistochemical staining for IgG4, Zhang et al. [12] reported that the sensitivity in resected AIP specimens was 72% (21/29). In the present study, there was one IgG4-negative AIP case, so it was considered just to be a supportive clue in resected pancreatic specimens.

During the same period, in comparison, a total of 145 patients with pancreatic ductal adenocarcinoma received pancreatic resection (107 pancreaticoduodenectomies, 36 distal pancreatectomies, and 2 total pancreatectomies). In other words, 9.4% (15/160) of patients with presumed pancreatic carcinoma had benign pancreatitis. Moreover, nearly half the cases of mass-forming chronic pancreatitis were shown to be AIP. It is thus considered that the focal type of AIP is by no means a rare clinical entity.

The results of pancreaticoduodenectomy in some high volume centers in western countries have been reported, and similarly, about 10% (11–13%) of cases were shown to be benign disease [19–21]. These studies also reported an 11–34% incidence of focal-type AIP out of resected so-called chronic pancreatitis. These studies, however, were different from our report essentially in two points: the type of resection was limited to only pancreaticoduodenectomy, and the population included every peripancreatic disease and disorder. Although chronic mass-forming pancreatitis resembles pancreatic ductal adenocarcinoma clinically and radiologically, most periampullary tumors, pancreatic endocrine tumors, and pancreatic cystic tumors are easily diagnosed with their characteristic findings. Therefore, we excluded these tumors in the present study and calculated the incidence of the focal type of AIP.

Sasson et al. [20] also reported that despite the advances in imaging modalities, the ability to discriminate between benign inflammatory conditions and neoplastic disease is still inadequate. Similarly, in our institution the incidence of resected AIP has not decreased, even in recent years.

The clinical presentations and radiological findings of focal-type AIP are similar to those of pancreatic malignancy, especially ductal adenocarcinoma;

Table III. Clinical, radiological and pathological findings in both resected AIP and mass-forming pancreatitis not otherwise specified.

| | | Focal-type AIP ($n=7$) | Mass-forming pancreatitis NOS ($n=8$) |
|---|---|---|---|
| Age | Mean (range) | 60.9 (51–68) | 49.6 (38–74) |
| Gender | Male:Female | 7:0 | 7:1 |
| Background | Alcohol abuse | 0/7 | 3/8 |
| | Autoimmune history | 0/7 | 0/8 |
| | Etiology | | Alcoholic: 3<br>Gallstones: 1<br>Not specified: 4 |
| Location | Head | 5/7 | 7/8 |
| Symptoms | Jaundice* | 4/5 | 2/7 |
| | Epigastralgia | 4/7 | 3/8 |
| CT | Delayed enhancement | 7/7 | 5/8 |
| | Capsule-like rim | 1/7 | 0/8 |
| | Cyst | 0/7 | 3/8 |
| | Calcification | 0/7 | 1/8 |
| MRP | MPD stenosis | 2/2 | 2/2 |
| ERP | MPD narrowing | 4/4 | 4/6 |
| Pathology | IgG4(+) plasma cells | 6/7 | 0/8 |

Abbreviations: NOS = not otherwise specified; AIP = autoimmune pancreatitis; CT = computed tomography; MRP = magnetic resonance pancreatography; ERP = endoscopic retrograde pancreatography.
*Patients with lesions of the pancreatic head.

therefore, some AIP patients have been treated surgically [22]. Regarding the favorable response of AIP to steroid therapy, accurate diagnosis is considered clinically important.

The characteristic features of pancreatic ductal adenocarcinoma have already been well documented and recognized. Jaundice, pain, and weight loss are its classic symptoms [23]. On dynamic CT, pancreatic ductal adenocarcinoma typically has the appearance of an ill-defined, hypoattenuating focal mass during the arterial phase when compared with the normal pancreatic parenchyma, along with diminished enhancement in the delayed phase [24,25]. Moreover, obstruction of the MPD on ERP is considered to be the most common pancreaticographic finding [25].

Recently, some characteristic findings of focal-type AIP have been reported to be useful in discriminating AIP from pancreatic carcinoma, such as the fluctuating course of jaundice [4], frequent association with other autoimmune disorders [1,10,11], raised serum levels of IgG4 [6,13], homogeneous delayed enhancement in dynamic CT, and longer MPD stenosis without upstream dilatation (maximum upstream diameter $<6$ mm) [5].

In the present study, 4 out of the 5 patients with pancreatic head lesions presented with obstructive jaundice, but fluctuation was not observed. In past medical history, there was no other autoimmune disease such as inflammatory bowel disease in any patient.

The serum level of IgG4, which was measured in only 2 patients, was raised. Although evaluation of serum IgG4 might be useful, it is not a definite diagnostic clue, as was recently reported in a case of pancreatic carcinoma with a high serum IgG4 concentration [26].

CT images showed delayed enhancement of the tumor to some extent in every patient. However, this finding indicates abundant fibrosis in the pancreatic parenchyma, which applies to both chronic pancreatitis and pancreatic ductal adenocarcinoma. Discrimination of these two entities according to the degree of enhancement is considered clinically impossible.

Irie et al. [27] reported that a capsule-like rim around the pancreas, reflecting the inflammatory process, was a typical sign of AIP. However, in the present study, only 1 out of 7 patients exhibited this feature in dynamic CT; therefore, a capsule-like rim might be less sensitive for the diagnosis of focal-type AIP.

To some extent post-stenotic dilatation of the MPD was detected in all patients with the exception of two; one had a tumor in the uncinate process, and the mass in the other patient was located in the body–tail of the pancreas; therefore, evaluation of the post-stenotic status was impossible. However, the maximal diameter was limited to within 5 mm in all patients as was previously reported [5].

Kamisawa et al. [28] reported the different appearance of MRP and ERP images in AIP patients; the narrowed portion of the MPD noticed on ERP was not visualized on MRP. Therefore, MRP cannot differentiate the irregular narrowing of the main pancreatic duct seen within AIP from stenosis of the MPD in pancreatic ductal adenocarcinoma.

Similarly, 4 patients who underwent ERP demonstrated irregular or smooth narrowing of the pancreatic duct; in contrast, 2 patients who recently underwent MRP exhibited obstruction of the MPD. Examination of the cut surface of the resected specimen in these two patients who underwent MRP confirmed that the narrowed MPD actually penetrated the tumor. Stenotic or obstructive findings of the MPD on MRP are not only characteristic of pancreatic carcinoma, but may be suggestive of AIP, because of the low resolution of MRP. Alternatively, ERP findings of AIP such as irregular or smooth narrowing of the pancreatic duct are considered to be diagnostic in order to differentiate AIP from pancreatic carcinoma.

In conclusion, about 10% of patients who were suspected of having pancreatic ductal adenocarcinoma and were subjected to surgical intervention had chronic pancreatitis in the clinical setting. Moreover, about half of the cases of resected chronic pancreatitis showed focal-type AIP. These findings suggest that the focal type of AIP is not a rare clinical entity, and undiagnosed cases might be buried in previously resected pancreatic specimens that in the past were diagnosed simply as mass-forming pancreatitis.

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Original contribution

# Primary tumor/vessel tumor/nodal tumor classification of extrahepatic bile duct carcinoma☆

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**Summary** Although the pathological tumor-node-metastasis (pTNM) classification is the histologic prognostic classification currently used clinically worldwide to predict the outcome of patients with extrahepatic bile duct carcinoma (EBDC), some patients with EBDC in the early pTNM stage experience tumor recurrence and some of them die of their disease. We have confirmed that the histologic characteristics of tumor cells and tumor stromal cells in the vessels and lymph nodes of patients with EBDC are more strongly associated with tumor recurrence or death than in the primary tumor. The purpose of this study was to establish a primary tumor/vessel tumor/nodal tumor (PVN) classification for EBDC that would accurately predict the outcome of 72 patients. Multivariate analyses using the Cox proportional hazard regression model were used to compare the ability of the PVN classification to predict tumor recurrence and death with that of the pTNM, the American Joint Committee on Cancer, and the Japanese pTNM classification systems; and the results showed that only the PVN classification significantly increased the hazard rates for tumor recurrence and death independent of nodal status ($P < .05$). We conclude that the PVN classification is *probably* the most accurate prognostic classification system available for EBDC.


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## 1. Introduction

Extrahepatic bile duct carcinoma (EBDC) is a fatal disease, and that has made it difficult to conduct a study that would accurately identify prognostic histologic parameters.

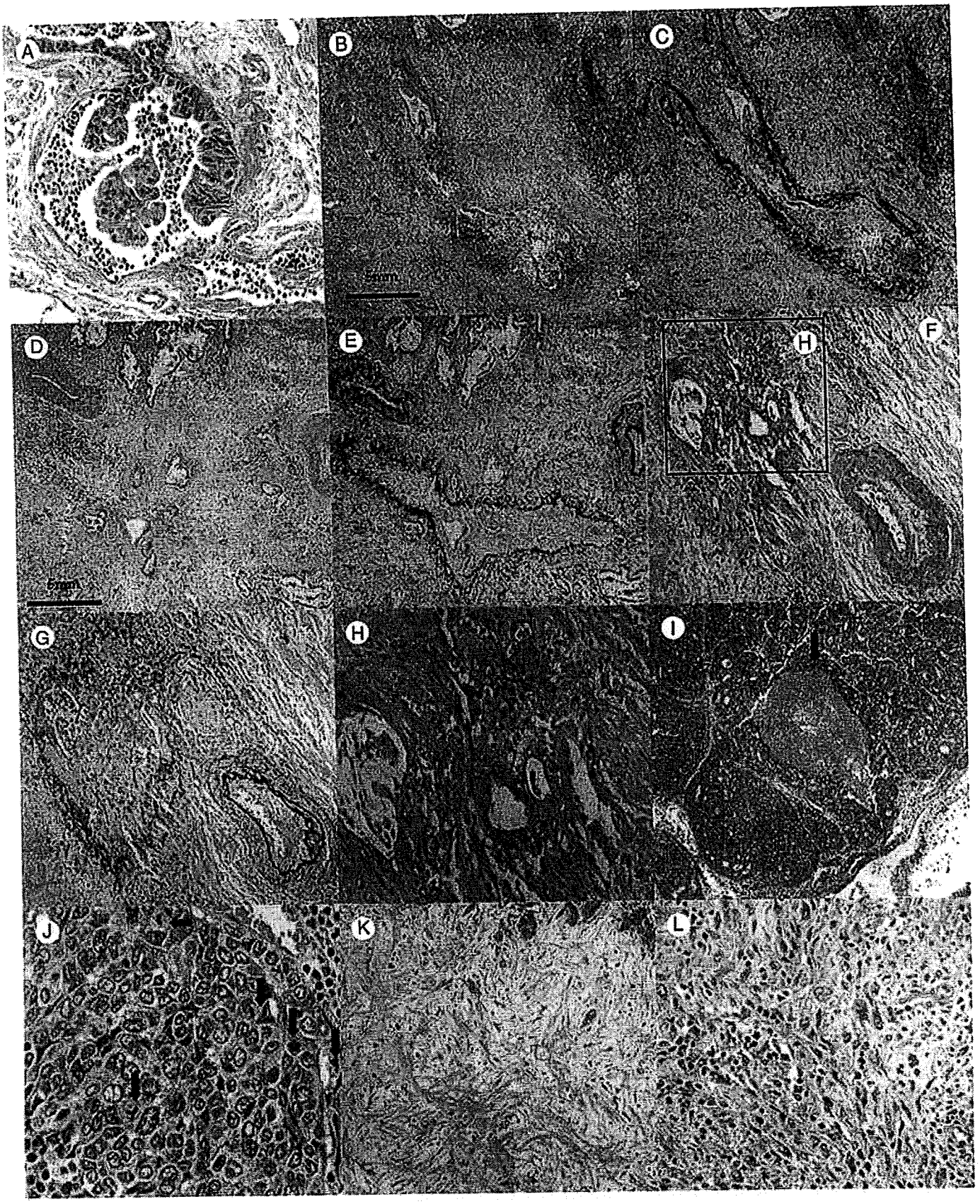
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Table 1 PVN classification of patient with EBDC

| 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 | | Overall survival | |
| | | Trend HRs/95% CIs/*P* | | 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

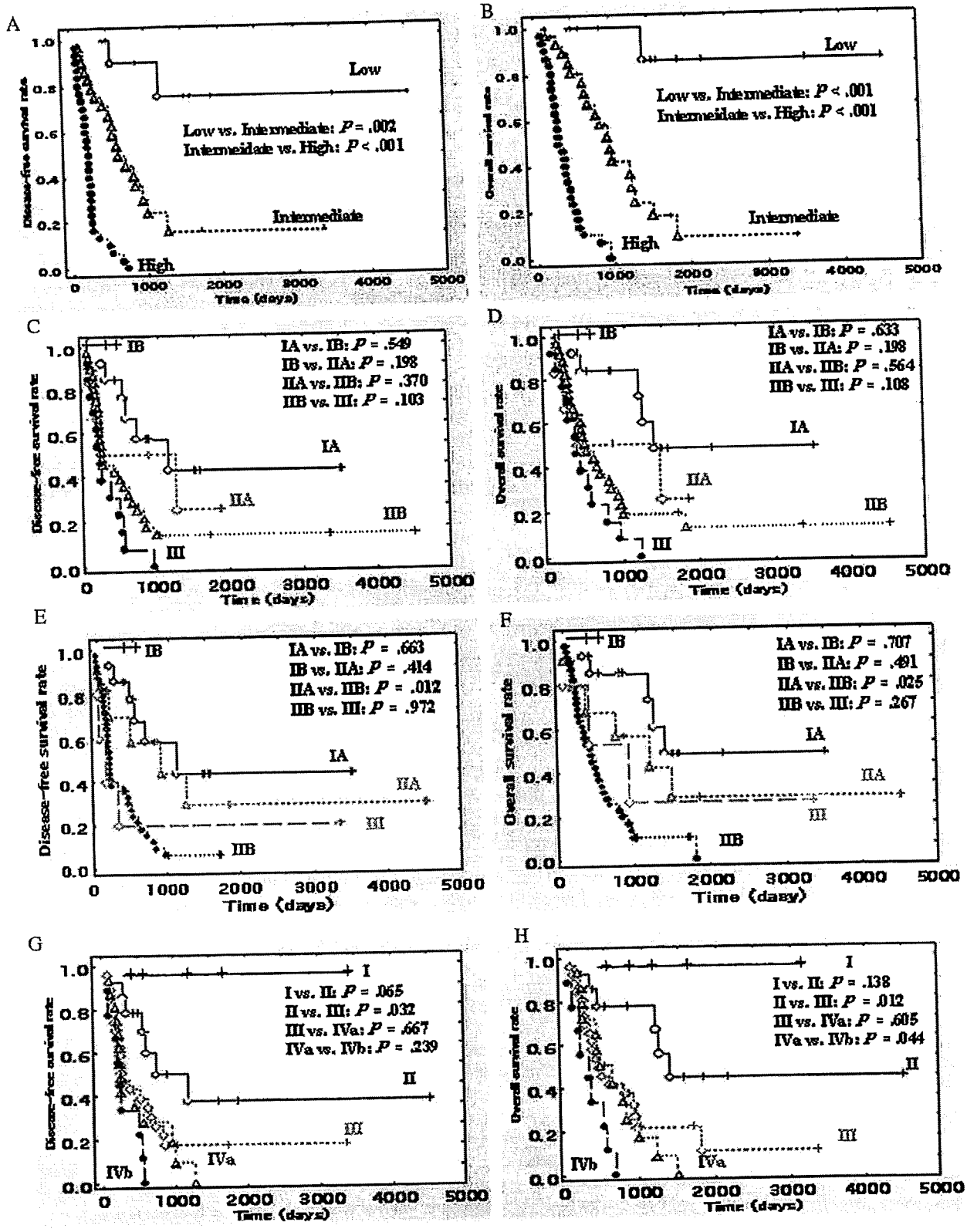
The following existing histologic classifications were compared with the PVN classification in regard to prediction of disease-free survival and overall survival: (1) pTNM [1], (2) AJCC [9], and (3) JpTNM [6]. Briefly, the JpTNM classification consists of T, N, and M categories. The T category is based 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

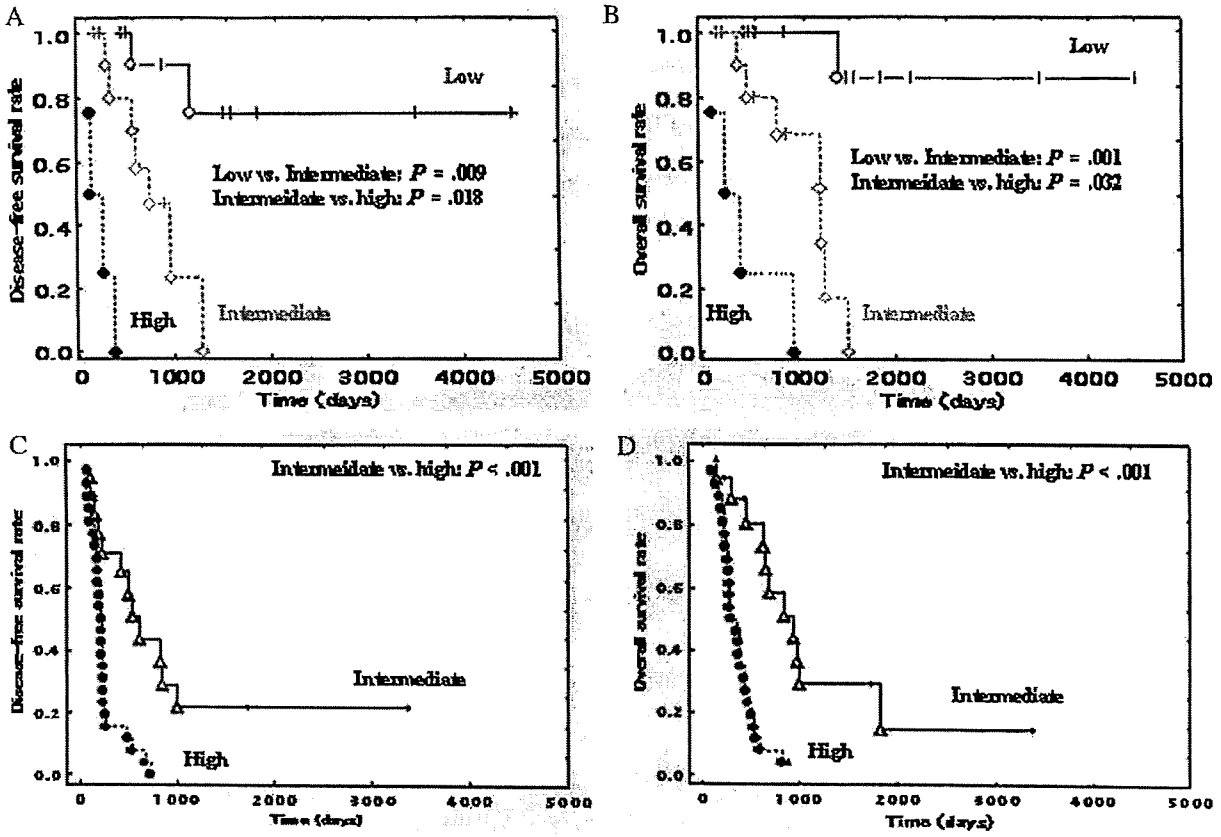



Fig. 3 Disease-free survival and overall survival curves according to the PVN classification of EBDCs according to nodal status. A and B, EBDCs without nodal metastasis. C and D, EBDCs with nodal metastasis. A to D, Disease-free survival time and overall survival time decreased according to the order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

**Table 4** (*continued*)

| 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.

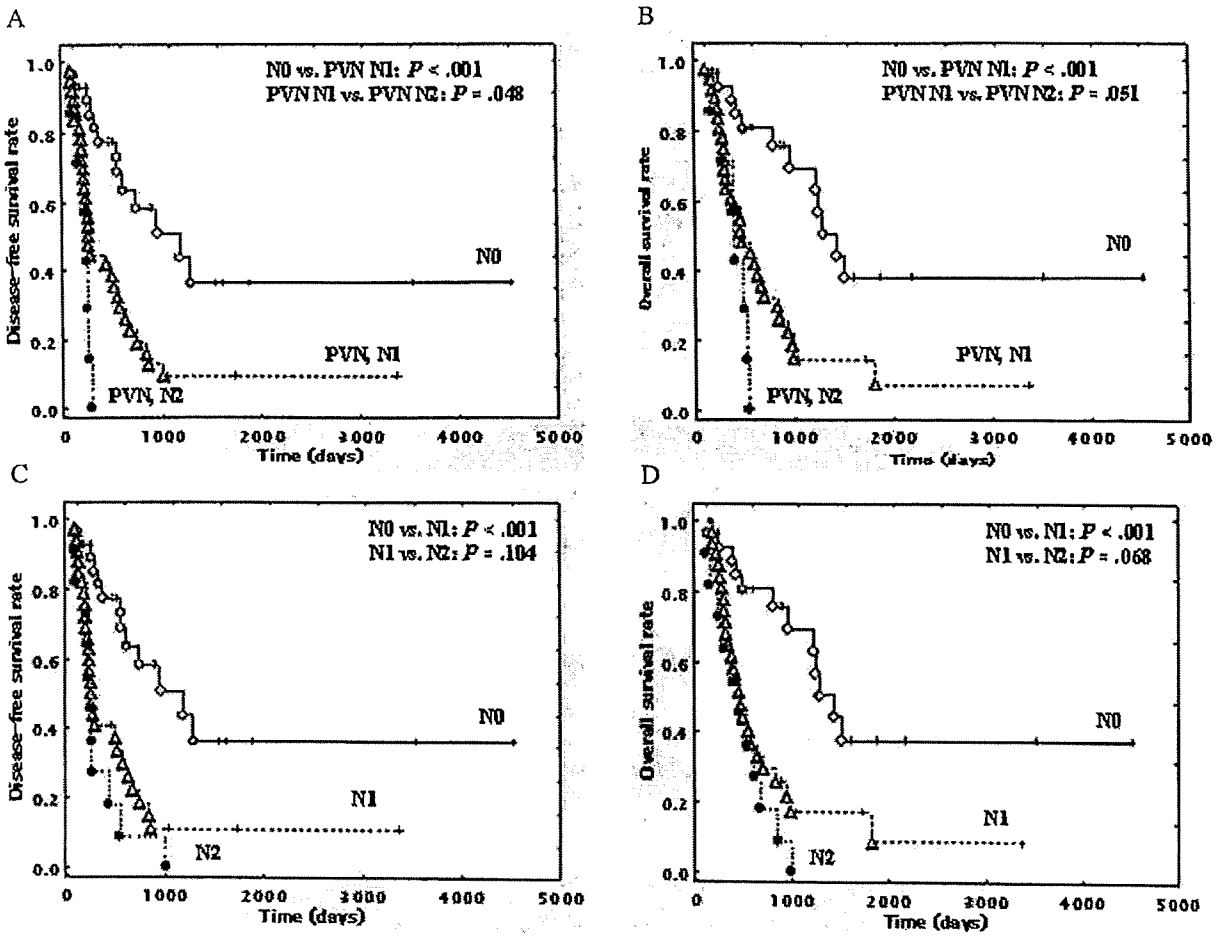



Fig. 4 Disease-free survival and overall survival curves according to the PVN nodal classification and the nodal classification of Hong et al of all patients with EBDC. A and B, Disease-free survival time and overall survival time in the risk categories in the PVN nodal classification decreased according 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.

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Original Paper

# Clinical Results of Extended Lymphadenectomy and Intraoperative Radiotherapy for Pancreatic Adenocarcinoma

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**KEY WORDS:**
Pancreatic adenocarcinoma; Invasive intraductal papillary mucinous adenocarcinoma; Extended lymphadenectomy; Intraoperative radiotherapy

**ABBREVIATIONS:**
Median Survival Time (MST); Recurrence-Free Survival Time (RFST); Intraductal Papillary Mucinous Tumor (IPMT); Intraoperative Radiotherapy (IORT)

## ABSTRACT

**Background/Aims:** The efficacy of extended lymphadenectomy and intraoperative radiotherapy for resectable pancreatic cancer is controversial. The objective of this study was to clarify the surgical outcome after pancreatic resection with extended lymphadenectomy or intraoperative radiotherapy in patients with pancreatic adenocarcinoma.

**Methodology:** Between 1992 and 2002, 105 patients with pancreatic adenocarcinoma undergoing surgical resection were retrospectively analyzed. Eighty-eight patients had invasive ductal adenocarcinoma and 17 had invasive intraductal papillary mucinous adenocarcinoma. Seventy-six patients underwent pancreatic resection with extended lymphadenectomy and 44 received 20 Gy intraoperative radiotherapy.

**Results:** Patients with invasive intraductal papillary mucinous adenocarcinoma had a similar prognosis to those with invasive ductal adenocarcinoma. There was no significant difference in survival ($p=0.86$) between patients with and without extended lymphadenectomy. There was no significant difference in survival ($p=0.053$) between patients with and without intraoperative radiotherapy. Patients without lymph node metastasis had a significantly better prognosis ($p=0.0015$) than those with nodal involvement.

**Conclusions:** Neither extended lymphadenectomy nor intraoperative radiotherapy showed a survival advantage in patients with resectable pancreatic adenocarcinoma. Pancreatic cancer patients without nodal involvement had a significantly better prognosis than those with nodal involvement.

## INTRODUCTION

Pancreatic cancer is one of the most devastating cancers. Although surgical resection offers the only chance of cure in patients with pancreatic adenocarcinoma, the long-term surgical outcome remains extremely poor. The five-year survival rate is 5-25% for patients undergoing potentially curative resection (1-6). Local recurrence and liver metastasis are the most common causes of death after surgical resection. In order to prevent local recurrence and improve postoperative survival, some therapeutic approaches, such as extended lymphadenectomy or intraoperative radiotherapy, have been performed and reported (7-13). Some authors reported better survival results after pancreatoduodenectomy with extended lymph node dissection (7,8). However, recent prospective randomized trials from Europe and the United States have demonstrated that extended lymphadenectomy with pancreatectomy does not appear to prolong survival (14,15). Other randomized trials showed no survival benefit of adjuvant chemoradiotherapy after pancreatic resection for pancreatic cancer (16,17). However, some authors reported that intraoperative radiotherapy achieved a significant improvement in local control and outcome in patients with locally limited pancreatic cancer (10,11). Thus, the efficacy of extended lymphadenectomy or intraoperative radiotherapy for resectable pancreatic cancer is still controversial. The objective of this study was to clarify the surgical outcome after pancreatic resection with extended lymphadenectomy or intraoperative radiotherapy in patients with pancreatic adenocarcinoma.

## METHODOLOGY

Between September 1992 and December 2002, 105 consecutive patients with pancreatic adenocarcinoma undergoing surgical resection at the National Cancer Center Hospital East were retrospectively analyzed. Patients with liver metastasis at laparotomy were excluded from this study. All 105 patients were followed after operation. Follow-up ranged from 0.7 to 102 months (median 12 months). The overall survival analysis included all deaths, such as in-hospital death or death from unrelated cause. Pancreatic adenocarcinomas were pathologically classified as invasive ductal adenocarcinoma (n=88) and invasive intraductal papillary mucinous adenocarcinoma (n=17). Lymph nodes were classified numerically according to the

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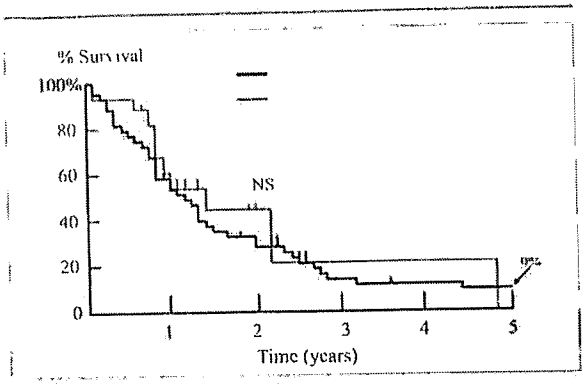


**FIGURE 1** Five-year survival rates for patients with invasive ductal adenocarcinoma (n=88) and for those with invasive intraductal papillary mucinous adenocarcinoma (n=17). The 1-, 3-, and 5-year actuarial survival rates were 53%, 14%, and 9% for patients with invasive ductal adenocarcinoma (n=88) and 55%, 22%, and 0% for those with invasive intraductal papillary mucinous adenocarcinoma (n=17), showing no significant difference ($p$=0.32).

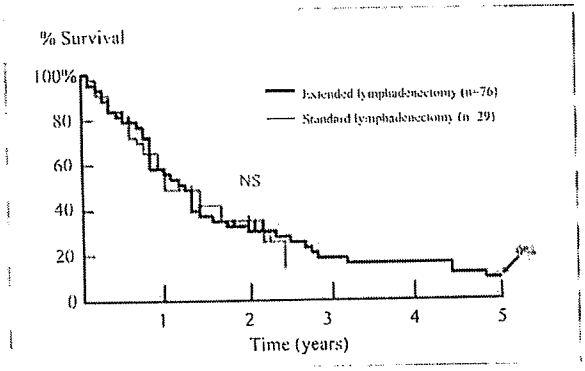


**FIGURE 2** Five-year survival rates for patients with (n=76) and without extended lymphadenectomy (n=29). There was no significant difference in survival between patients with extended lymphadenectomy and those with standard lymphadenectomy ($p$=0.86).

Japanese classification of pancreatic carcinoma proposed by the Japan Pancreas Society (18).

Patients underwent pancreatic resection with standard or extended lymphadenectomy without random allocation. Standard lymphadenectomy for pancreatic head cancer included removal of the anterior and posterior pancreatoduodenal lymph nodes (No. 17, 13) and nodes along the cystic duct and distal bile duct (No. 12b). In addition to standard lymphadenectomy, extended lymphadenectomy for pancreatic head cancer included removal of nodes along the superior mesenteric artery (No. 14p, 14d), nodes along the common hepatic artery (No. 8a, 8p), hepatoduodenal ligament nodes (No. 12b, 12a, 12p), inferior pyloric lymph nodes (No. 6), celiac nodes (No. 9), and nodes along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery (No. 16a2, 16b1) **(Figure 5)**. Standard lymphadenectomy for pancreatic body or tail cancer included removal of the nodes along the splenic artery (No. 11p, 11d), nodes at the splenic hilum (No. 10), nodes along the common hepatic artery (No. 8a, 8p), and inferior pancreatic nodes (No. 18). In addition to standard lymphadenectomy, extended lymphadenectomy for pancreatic body or tail cancer included removal of nodes along the superior mesenteric artery (No. 14p, 14d), nodes along the left gastric artery (No. 7), celiac nodes (No. 9), lower hepatoduodenal ligament nodes (No. 12b, 12p, 12a), and nodes along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery (No. 16a2, 16b1).

Forty-four patients with pancreatic adenocarcinoma were treated with 20 Gy of intraoperative radiotherapy immediately after removal of the primary pancreatic tumor. An electron beam energy of 6-12 MeV was used to deliver 20 Gy to the treatment field including the dissected retropancreatic connective tissue, the root of the celiac axis and the root of the superior mesenteric artery.

Statistical analysis was performed by chi-squared and Student's $t$-test, as appropriate. Cumulative survival rates were generated by Kaplan-Meier method. The survival curves were compared by generalized Wilcoxon test. Differences were considered significant at $p<0.05$.

## RESULTS

Among the patients with pancreatic adenocarcinoma, 84% (88/105) had invasive ductal adenocarcino-

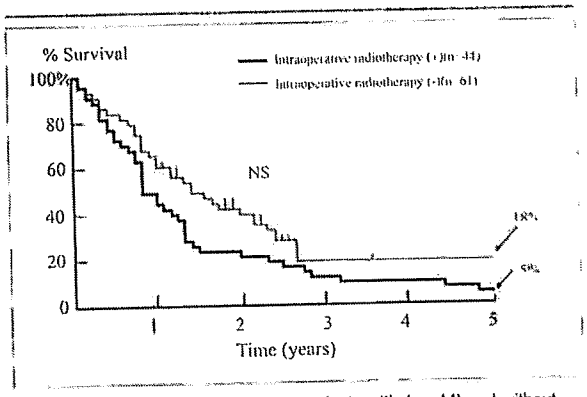


**FIGURE 3** Five-year survival rates for patients with (n=44) and without intraoperative radiotherapy (n=61). There was no significant difference in survival ($p$=0.053) between the patients with and without intraoperative radiotherapy.

**TABLE 1 Characteristics of Ductal Carcinoma and Invasive Intraductal Papillary Mucinous Tumors**

| Characteristics | | Ductal carcinoma (n=88) | Invasive IPMT (n=17) |
|---|---|---|---|
| Age (years), mean | | 63 | 68 |
| Gender (male/female) | | 50/38 | 12/5 |
| Tumor size (cm), mean | | 3.8 (range 1.5-12.0) | 5.7 (range 3.5-12.2) |
| Location | Head | 66 | 14 |
| | Body and/or Tail | 22 | 3 |
| Nodal involvement (%) | | 79 (90%) | 10 (59%) |
| Involved margin (%) | | 20 (23%) | 6 (35%) |
| Extended lymphadenectomy | Yes | 68 | 8 |
| | No | 20 | 9 |
| Intraoperative radiotherapy | Yes | 40 | 4 |
| | No | 48 | 13 |

IPMT: intraductal papillary mucinous tumor.

**TABLE 2 Characteristics of Patients with Standard Lymphadenectomy and Extended Lymphadenectomy**

| | | Standard Lymphadenectomy (n=29) | Extended Lymphadenectomy (n=76) |
|---|---|---|---|
| Age (years), mean | | 69 | 61 |
| Gender (male/female) | | 19/10 | 43/33 |
| Type of cancer | Ductal cancer | 20 | 68 |
| | Invasive IPMT | 9 | 8 |
| Lymph node metastasis | | 23 (79%) | 66 (87%) |
| Involved margin | | 13 (45%) | 13 (17%) |
| Pancreatic margin | | 2 (7%) | 5 (7%) |
| Dissected peripancreatic tissue | | 11 (38%) | 9 (12%) |
| Intraoperative radiotherapy | Yes | 4 | 40 |
| | No | 25 | 36 |

ma. The characteristics of the patients with invasive ductal adenocarcinoma and invasive intraductal papillary mucinous adenocarcinoma are shown in **Table 1**. The mean age of patients with invasive ductal adenocarcinoma and invasive intraductal papillary mucinous adenocarcinoma was 63 and 68 years, respectively. The mean size of invasive ductal adenocarcinoma and invasive intraductal papillary mucinous adenocarcinoma was 3.8cm (range: 1.5-12.0) and 5.7cm (range: 3.5-12.2), respectively, showing a significant difference ($p$=0.011). In invasive ductal adenocarcinoma, 75% of tumors were located in the head of the pancreas (66/88), while 82% of intraductal papillary mucinous adenocarcinomas were located in the head of the pancreas (14/17).

Patients with pancreatic adenocarcinoma were treated by pylorus-preserving pancreatoduodenectomy (n=56), subtotal stomach-preserving pancreatoduodenectomy (n=17), Whipple's pancreatoduodenectomy (n=5), total pancreatectomy (n=2), duodenum-preserving pancreatic head resection (n=1), or distal pancreatectomy (n=24).

Overall, the rate of lymph node metastasis was 85% for all pancreatic adenocarcinomas (89/105). The frequency of nodal involvement for invasive ductal adenocarcinoma and invasive intraductal papillary mucinous adenocarcinoma was 88% (67/76) and 59% (10/17), respectively. Lymph node metastasis was observed in 79% of patients with standard lymphadenectomy and 87% of patients with extended lymphadenectomy (**Table 2**). For the standard lymphadenectomy group, the mean total number of resected lymph nodes was 27. For the extended lymphadenectomy group, the mean total number of sampled lymph nodes was 49. There was a significant difference ($p$=0.001) between the groups. The surgical margin was positive in 45% of patients with standard lymphadenectomy (13/29) and 17% of patients with extended lymphadenectomy (13/76). Overall, 25% of patients with pancreatic adenocarcinoma (26/105) had a positive margin. The dissected peripancreatic margin was involved in 20 patients (11 with standard lymphadenectomy and 9 with extended lymphadenectomy), and the pancreatic margin was involved in 7 patients (2 with standard lymphadenectomy and 5 with extended lymphadenectomy).

The overall 1-, 3-, and 5-year survival rates for all 105 patients with pancreatic adenocarcinoma were 53%, 16%, and 8%, respectively. The 1-, 3-, and 5-year actuarial survival rates were 53%, 14%, and 9% for patients with invasive ductal adenocarcinoma (n=88) and 55%, 22%, and 0% for those with invasive intraductal papillary mucinous adenocarcinoma (n=17) (**Figure 1**), showing no significant difference ($p$=0.32). The 5-year survival rate for patients with (n=76) and without extended lymphadenectomy (n=29) was 9% and 0%, respectively (**Figure 2**), showing no significant difference in survival between patients with extended lymphadenectomy and those with standard lymphadenectomy ($p$=0.86). There were no significant differences in both median survival time (MST) and recurrence-free survival time (RFST) between standard lymphadenectomy group (MST: 12 months, RFST: 9 months) and extended lymphadenectomy group (MST: 14 months, RFST: 9months). To exclude the influence of IORT, survival rates for standard lymphadenectomy group without IORT (n=25) and extended lymphadenectomy group

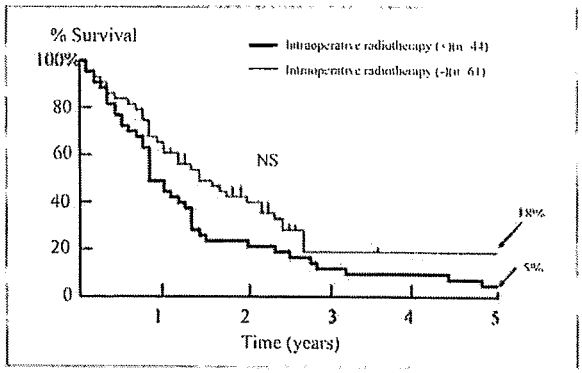


**FIGURE 3** Five-year survival rates for patients with (n=44) and without intraoperative radiotherapy (n=61). There was no significant difference in survival ($p$=0.053) between the patients with and without intraoperative radiotherapy.

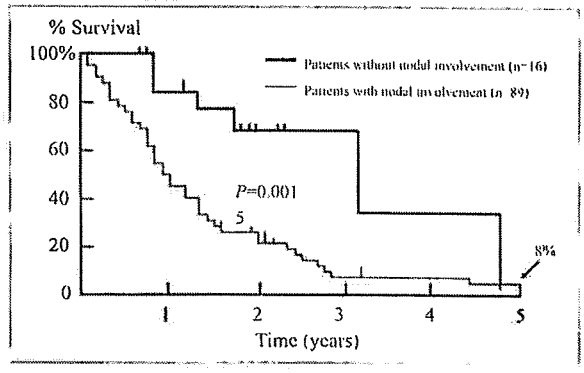


**FIGURE 4** Five-year survival rates for patients with (n=89) and without lymph node involvement (n=16). There was a significant difference between the patients with and without lymph node involvement ($p$=0.0015). The median survival of patients with and without nodal involvement was 12 and 38 months, respectively.