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Clinicopathologic Factors Influencing Survival of Patients with Bile Duct Carcinoma: Multivariate Statistical Analysis

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To evaluate the influence of various clinicopathologic factors on survival, a computer analysis was performed on 70 patients who underwent resection for bile duct carcinoma. Univariate analysis of overall survival involving all the patients identified 10 factors that were associated with a significant outcome: location of primary lesion ($p = 0.01$), pancreatic invasion ($p = 0.004$), duodenal invasion ($p = 0.005$), macroscopic and microscopic vascular involvement ($p = 0.009$ and $p = 0.04$), perineural invasion ($p = 0.02$), lymphatic vessel involvement ($p = 0.04$), lymph node metastasis ($p = 0.02$), histologic type ($p = 0.02$), and depth of cancer invasion ($p = 0.04$). However, when the interactive effects of these factors were taken into account, the pancreatic invasion and perineural invasion were selected as the two most significant prognostic factors in a multivariate analysis using the Cox stepwise proportional hazards model. The age, sex, size of the tumor, macroscopic type of lesions, hepatic infiltration, serosal invasion, resected surgical margin at the proximal and distal ends, exposed surgical margin, peritoneal dissemination, and hepatic metastasis were not significantly associated with prognosis.

With the recent improvement of surgical techniques in hepatobiliary surgery, a curative surgical resection of the bile duct carcinoma can be accomplished with reasonable morbidity and mortality [1, 2]. However, the prognosis for such patients is frustrating particularly in cases of carcinoma of the hepatic hilus, although this tumor is small, is slow-growing, and metastasizes late [3]. Resection of these difficult lesions offers the best hope of survival [4, 5]. Previously, Tompkins et al. [6] demonstrated the prognostic factors affecting survival of the patient with bile duct carcinoma, but they did not use the Cox proportional hazards model [7] for analysis.

In the present article, an effort is made to evaluate the influence of various clinicopathologic factors on survival of patients with bile duct carcinoma by using the Cox proportional hazards model. The results of these analyses are used when recommending rational surgical treatment for patients with bile duct carcinoma.

Materials and Methods

This study was conducted on 70 patients whose bile duct carcinomas were resected at the First Department of Surgery, Nagoya University Hospital from January 1979 through September 1990. All the lesions were resected after preoperative precise diagnosis. The resected specimens were examined and the relation between clinicopathologic findings and patient survival was studied. After operation the patients were followed routinely. Average follow-up was 66.5 months (range 21–133 months).

Variables

The following clinicopathologic variables were considered for prognostic effect: age, sex, location of primary tumor (upper, middle, and lower bile duct carcinoma), size of the tumor, macroscopic type of lesion (papillary, nodular, nodular infiltrating, infiltrating), serosal invasion (present or absent), peritoneal dissemination (present or absent), hepatic metastasis (present or absent), lymph node metastasis (present or absent), hepatic infiltration (present or absent), pancreatic invasion (present or absent), duodenal invasion (present or absent), macroscopic vessels involvement (present or absent), microscopic vessels involvement (present or absent), lymphatic vessels involvement (present or absent), perineural invasion (present or absent), resected proximal margin of the bile duct (cancer positive or negative), resected distal margin (cancer positive or negative), exposed surgical margin (cancer positive or negative), histologic type of lesion (papillary adenocarcinoma, well differentiated adenocarcinoma, moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, and adenosquamous cell carcinoma), depth of cancer invasion (invasion limited to fibromuscular layer, invasion limited to adventitia and subserosal layer, invasion to and beyond the serosal layer).

Analysis

Independent variables were first analyzed by univariate methods. Statistical significance of the variables were determined by the Student *t*-test and the chi-square test. Survival for each variable was estimated by the method of Kaplan and Meier, and the significance of survival was determined by the generalized Wilcoxon method. Only the variables that were statistically

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significant by univariate analysis were included in a multivariate analysis. The multivariate results were confirmed using the Cox stepwise proportional hazard model.

Results

Clinical Findings

Of the 70 operated patients, 48 were men and 22 were women. Average age at the time of operation was 57.5 years (range 32–82 years). Of the lesions, 52 (74.3%) were upper bile duct cancer, 8 (11.4%) were middle bile duct cancer, and 10 (14.3%) were lower bile duct cancer. All the lesions were resected at operation. Curative resection was done for 51 patients and noncurative for 19 patients. The site and extent of tumor influenced the type of operation. Bile duct resection was done in 2 patients, hepatectomy with bile duct resection in 46, pancreatoduodenectomy in 18, and hepatopancreatoduodenectomy [8] in 4.

Overall Survival

Univariate Analysis. The 5-year survival rate for all patients was 25%. Twenty-one clinicopathologic factors were analyzed, and the prognosis was significantly related to 10 of the 21 variables analyzed by univariate method (Table 1). The significant variables were location of primary tumor, microscopic type of tumor, depth of cancer invasion, perineural invasion, macroscopic and microscopic vessels involvement, lymphatic invasion, lymph node metastasis, duodenal invasion, and pancreatic invasion. The following factors were not significantly associated with prognosis: age, sex, size of the primary lesion, macroscopic type of tumor, peritoneal dissemination, hepatic metastasis, hepatic infiltration, resected surgical margin, and exposed surgical margin.

Multivariate Analysis. Multivariate analysis using the Cox proportional hazards model involving the 10 significant factors determined by univariate analysis identified the two most prognostic variables (Table 2). They were the pancreatic invasion and the perineural invasion.

Pancreatic Invasion and Survival. Pancreatic invasion was observed in 14 (20%) of the 70 patients with bile duct carcinoma. It was observed in 6 of 10 (60%) of those with lower bile duct cancer, 4 of 8 (50%) with middle bile duct cancer, and 4 of 52 (8.3%) with upper bile duct cancer. Pancreatic invasion was the first prognostic variable detected by the Cox stepwise proportional hazards model (Table 2). The 3- and 5-year survival rates for patients with negative pancreatic invasion were 52% and 46%, respectively. There were no 5-year survivors among patients with positive pancreatic invasion (Fig. 1). A statistically significant difference in survival could be observed between the patient with positive and negative pancreatic invasion ($p = 0.005$). The death risk for patient with positive pancreatic invasion was 2.4 times greater than that for the patient with negative pancreatic invasion.

Perineural Invasion and Survival. Perineural invasion was seen in 82.8% of the patients with bile duct cancer. Univariate

Table 1. Univariate analysis of the clinicopathologic factors.

Factor	No. of patients	P value
Age		0.33
Sex		0.90
Male	48	
Female	22	
Location of tumor		0.01
Upper	52	
Middle	8	
Lower	10	
Size of tumor		0.98
Macroscopic type of lesions		0.43
Papillary	14	
Nodular	22	
Nodular infiltrating	10	
Infiltrating	24	
Serosal invasion		0.08
Present	21	
Absent	49	
Hepatic metastasis		0.88
Present	1	
Absent	69	
Peritoneal dissemination		0.06
Present	1	
Absent	69	
Lymph node metastasis		0.02
Present	30	
Absent	40	
Duodenal invasion		0.005
Present	10	
Absent	60	
Hepatic invasion		0.36
Present	29	
Absent	41	
Pancreatic invasion		0.004
Present	14	
Absent	56	
Macroscopic vessel involvement		0.04
Present	14	
Absent	56	
Microscopic vessel involvement		0.009
Present	53	
Absent	17	
Lymphatic vessel involvement		0.04
Present	63	
Absent	7	
Perineural invasion		0.01
Present	57	
Absent	13	
Resected proximal margin of the bile duct		0.95
Cancer positive	19	
Cancer negative	51	
Resected distal margin of the bile duct		0.95
Cancer positive	2	
Cancer negative	68	
Histologic type of lesion		0.02
Papillary adenocarcinoma	6	
Well differentiated adenocarcinoma	22	
Moderately differentiad adenocarcinoma	39	
Poorly differentiated adenocarcinoma	2	
Adenosquamous cell carcinoma	1	
Depth of cancer invasion		0.04
Invasion limited to fibromuscular layer	7	
Invasion limited to adventitia and subserosal layer	48	
Invasion to and beyond the serosal exposure	15	
Exposed surgical margin		0.92
Cancer positive	42	
Cancer negative	28	

Table 2. Relative values of two prognostic variables derived from Cox stepwise proportional hazards model.

Variable	β	SE	χ^2	p	HR	95% CI
Pancreatic invasion	0.89	0.33	7.01	0.008	2.40	(1.22–4.75)
Perineural invasion	1.01	0.44	5.25	0.02	2.76	(1.16–6.55)

Model chi-square = 13.28 (p = 0.001).
SE: standard error; χ^2: chi-square; HR: hazard ratio; CI: confidence interval.
Pancreatic invasion and perineural invasion: 0 = negative, 1 = positive.
Variables: This model included all the statistically significant variables identified by the univariate analysis shown in Table 1.

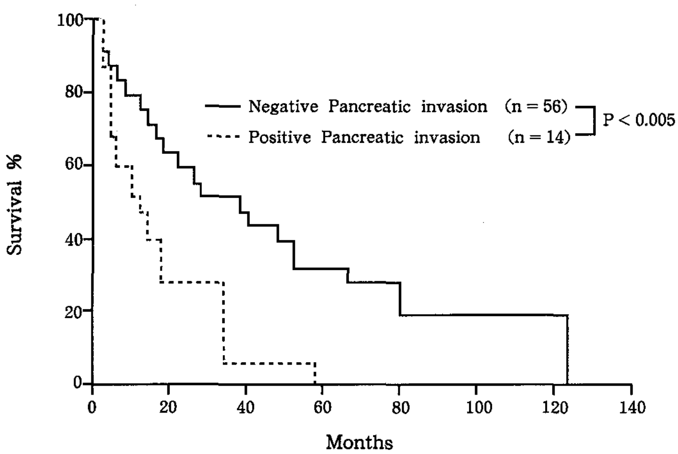

Fig. 1. Postoperative survival curves according to the presence or absence of pancreatic invasion. Differences between the groups are statistically significant ($p < 0.005$).

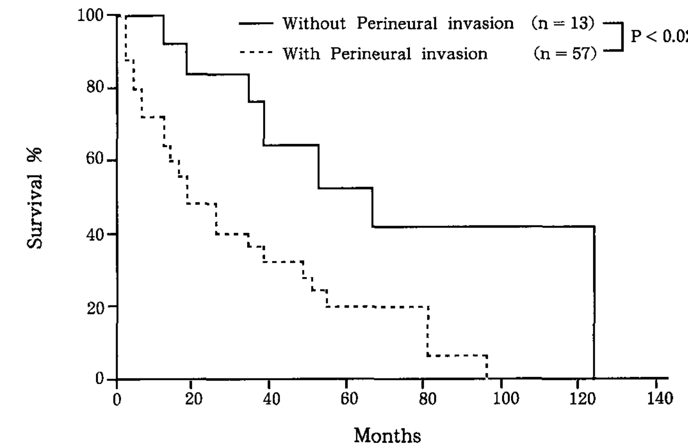

Fig. 2. Survival curves of the bile duct cancer patients according to the presence or absence of perineural invasion. A statistically significant difference of survival is seen between the patients with and without perineural invasion ($p < 0.02$).

Table 3. Pearson's correlation coefficients among variables: coefficients value (probability value).

Variable	Location of primary lesion
Perineural invasion	−0.201016 0.0806
Pancreatic invasion	0.38419 0.001

analysis showed a statistically significant difference of survival between the perineural invasion and perineural noninvasion groups (p = 0.02) (Table 1). The 3- and 5-year survival rates for patients without perineural invasion were 84% and 52%, respectively, whereas the perineural invasion-positive patients showed 40% and 19% survival, respectively (Fig. 2). The Cox stepwise proportional hazards model detected the perineural invasion as the second significant prognostic variable for bile duct cancer patient (Table 2). The perineural invasion patient had a 2.76 times greater death risk than did the perineural noninvasion patient.

Pancreatic Invasion and Perineural Invasion Versus Location of Primary Lesion. Pancreatic invasion was significantly correlated with the location of the primary lesion (p = 0.001) (Table 3). It was observed significantly in the lower and middle bile duct cancer. However, the perineural invasion was not associated with the location of the primary lesion. Therefore the perineural invasion was the independent prognostic factor irrespective of site.

Discussion

With the continual progress of diagnostic and surgical techniques in biliary surgery, a good number of biliary cancers can be resected with reasonable of morbidity and mortality [1]. The local recurrence of bile duct cancer is relatively high even after curative resection of this lesion. Therefore a suitable surgical procedure should be considered for preventing this undesirable outcome.

It is important to know what prognostic factors relate to the survival of the patient with bile duct cancer. Until now, no reports have appeared in the world literature using the Cox stepwise proportional hazards model to identify the best prognostic variables in patients with bile duct carcinoma. Tompkins et al. [6] analyzed the prognostic variables of the bile duct cancer patient, but they did not use the Cox proportional hazards analytic method. This analysis has now identified the two independent prognostic variables of bile duct cancer patient.

Pancreatic invasion is the first prognostic variable [hazard ratio (HR) = 2.40; p = 0.008] (Table 2). Patients with negative pancreatic invasion survived significantly better than those with positive pancreatic invasion after resecting the lesion. Our finding showed that the 5-year survival rate for patients with negative pancreatic invasion was 46%, whereas it was 0% for patients with positive pancreatic invasion. This poor prognosis might be due to the fact that when the bile duct cancer invades pancreatic tissue it behaves like a primary pancreatic cancer and leads to a worse prognosis. The risk of death for patients with positive pancreatic invasion was 2.4 times more than for patients with negative pancreatic invasion.

Perineural invasion was determined to be the second prognostic variable by the multivariate analysis (HR = 2.76; p = 0.02) (Table 2). We had previously studied extensively the clinicopathologic significance of perineural invasion [9], and the results of the present study substantiated those findings. The perineural noninvasion group showed a significantly better prognosis than the perineural-invasion group ($p = 0.02$) (Fig. 2). The death risk for patients with perineural invasion group was 2.76 times greater than for patients without perineural invasion.

Patients with lower bile duct cancer had a better survival rate after resection than did patients with middle and upper bile duct cancer. This finding substantiated findings reported by others [6]. However, patients with upper bile duct cancer showing relatively good postoperative survival compared to those with middle bile duct cancer, a finding that differs from those of previous authors. Preoperative precise diagnosis and appropriate hepatic segmentectomy [1] may be the reason for better survival of our patients with upper bile duct cancer.

Those with cancer invasion limited to the fibromuscular layer showed significantly better postoperative survival than did patients with cancer invasion to or beyond the adventitial layer ($p = 0.04$). Moreover, those with cancer invasion to or beyond the serosa showed the worst prognosis. Therefore bile duct cancer can be staged according to the depth of cancer invasion. Cancers whose invasion is limited to the fibromuscular layer of the bile duct may be defined as early bile duct cancers and cancers that have invaded beyond the fibromuscular layer as advanced cancer.

Beazly et al. [5] and Tompkins et al. [6] demonstrated several factors responsible for a favorable outcome in their patients with bile duct carcinoma, but they did not mention pancreatic and perineural invasion as prognostic factors. According to White [10], blood vessel invasion and perineural invasion were not prognostic factors for survival of the patient with bile duct carcinoma. We and many others [9, 11–14], however, have pointed out a significant correlation between perineural invasion and postoperative survival.

Findings from this study showed that the prognosis for patients with bile duct cancer is significantly associated with pancreatic invasion, perineural invasion, location of the primary lesion, histologic type of the lesion, macroscopic and microscopic vessel involvement, depth of cancer invasion, lymphatic invasion, lymph node metastasis, and duodenal invasion. Age, sex, size of the lesion, macroscopic type of lesion, serosal invasion, hepatic infiltration, peritoneal dissemination, hepatic metastasis, exposed surgical margin, and resected surgical margin were not significantly associated with survival.

Cameron et al. [4] and Hayes et al. [15] have advocated adjuvant radiotherapy as beneficial. On the other hand, hepatic transplantation has been attempted in the past at several centers with little success, although Pichlmayr et al. [16] have demonstrated encouraging results. We think that effective adjuvant therapy, if properly directed, can prevent an undesirable outcome.

According to this study, patients with positive pancreatic invasion had the worst prognosis; thus pancreatic invasion is the most significant prognostic factor for patients with bile duct cancer. This relation was observed most significantly in those with lower and middle bile duct cancer. Perineural invasion is the second most significant prognostic factor for bile duct cancer patients; in fact, perineural invasion implies a hopeless prognosis. It was an unfavorable prognostic factor irrespective of the site of the lesion.

We have already emphasized [9] the need for dissection of autonomic nerve fibers and plexuses around the hepatic and celiac arteries and the portal vein. In addition the lymph nodes, lymphatic vessels, and connective tissue must be dissected if the operation for bile duct carcinoma is to be curative. This retrospective study revealed the worst prognosis for patients with both perineural and pancreatic invasion, their death risk being 6.65 times higher than in those who had no such invasion. Therefore suitable adjuvant therapy should be considered together with the surgical procedure in cases of positive pancreatic and perineural invasion. This subject, however, warrants further study.

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Résumé

Afin d'évaluer l'influence de facteurs clinicopathologiques sur la survie, on a analysé les résultats observés chez 70 patients ayant un cancer des voies biliaires. L'analyse monofactorielle a permis d'identifier 10 facteurs pronostiques influençant la survie: site de la tumeur primitive (p = 0.01), envahissement du pancréas (p = 0.005), envahissement du duodénum (p = 0.005), envahissement vasculaire macro ou microscopique (p = 0.009 et p = 0.04, respectivement), envahissement périneural (p = 0.02), envahissement lymphatique (p = 0.04), envahissement ganglionnaire (p = 0.02), le type histologique (p = 0.02) et la profondeur de l'envahissement (p = 0.04). Par l'analyse multifactorielle selon la méthode pas à pas de Cox, les deux facteurs ayant la valeur pronostique la plus importante étaient l'envahissement pancréatique et périneural. Le sexe et l'âge du patient, la taille et l'aspect macroscopique de la tumeur, l'infiltration hépatique, l'envahissement de la séreuse, la marge de sécurité de la résection ainsi que les disséminations péritonéale et hépatique n'influencaient pas significativement le pronostic.

Resumen

Con el propósito de evaluar el impacto de los diferentes factores clinicopatológicos sobre la supervivencia, se realizó un análisis computadorizado en 70 pacientes sometidos a resección por carcinoma de la vía biliar. El análisis univariable de la supervivencia global aplicado a la totalidad de los pacientes identificó diez factores asociados con un desenlace significativo: la ubicación de la lesión primaria (P = 0.01), la invasión pancreática (P = 0.05), la invasión duodenal (P = 0.005), la invasión vascular tanto macroscópica como microscópica (P = 0.009 y P = 0.04), la invasión perineural (P = 0.02), la invasión de vasos linfáticos (P = 0.04), las metástasis a los ganglios linfáticos (P = 0.02), el tipo histológico (P = 0.02) y la profundidad de la invasión cancerosa (P = 0.04). Sin embargo, al tomar en cuenta el efecto interactivo de tales factores, se seleccionaron la invasión pancreática y la invasión perineural como los dos principales factores de pronóstico en un análisis multivariable utilizando el modelo de Cox de riesgos proporcionales escalonados. En tanto que la edad, sexo, tamaño del tumor, tipo macroscópico de la lesión, infiltración hepática, invasión de la serosa, márgenes de resección, diseminación peritoneal y metástasis hepáticas no resultaron asociadas con el pronóstico en forma significativa.

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Invited Commentary

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The authors have one of the largest series of resected bile duct tumors in the world. Their resectability rate is also one of the highest. This paper is very important for both of these reasons.

It is a pity that the results of upper-, middle-, and lower-third lesions have not been presented separately. The results of lower-third lesions are much better than the other two and significantly different [1]. Normally the results of middle- and upper-third lesions are very similar, except in this series.

Several features are remarkable. There is no significant difference in the macroscopic type of the lesion, in the degree of hepatic invasion, or in the presence of clear proximal or distal margins of the bile duct. It is also my feeling that it is impossible to ascertain that the margin is clear. Moreover, the diagnosis of cancer can be made during surgery and then be found to be erroneous after surgery in the final pathological report. Therefore, we cannot rule out surgical resection on pathological grounds only.

More explanation concerning pancreatic invasion would have been helpful, as it appears to be one of the most important prognostic factors. The authors' data on pancreatic invasion in upper third bile duct cancer is somewhat difficult to understand. How did they determine pancreatic invasion in the resected specimen in these upper-third cancers? Were the combined resections, including a Whipple procedure, done for this group? If so, could the reason be two contiguous lesions, or a diffuse lesion (and not an upper-third lesion), or a secondary lesion? In one of our cases, a cluster resection followed by liver transplantation was performed for an upper-third bile duct cancer, and we found an additional lower-third cancer [2]. It is possible that their previously described use of preoperative cholangioscopy permitted better assessment of upper-third bile duct cancer and a higher curative resection rate. We have previously shown that there is a significant survival difference depending upon the depth of cancer invasion and the TNM classification [1].

The use of adjuvant radiotherapy is very controversial. Van der Heyde et al. [3] showed a significant difference when postoperative radiotherapy (iridium and external radiotherapy) was associated with surgery. Yet, Cameron et al. [4] did not show any difference when radiotherapy was associated with curative resections—differences occurred only after palliative resections.

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