

Original scientific article

Characteristics of Bile Duct Carcinoma with Superficial Extension in the Epithelium

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Abstract

Background Longitudinal tumor extension from the main tumor involves intramural or superficial spread along the bile duct, which closely influences surgical curability. Identifying the range of superficial extension is difficult by preoperative imaging. To clarify specific characteristics of bile duct carcinoma (BDC) with superficial extension of epithelium in the bile duct, we examined clinicopathological features and patient outcomes in BDC patients with or without superficial extension who underwent surgical resection.

Methods Between 1994 and 2008, we retrospectively examined clinicopathological findings and outcomes for 42 BDC patients who underwent surgical resection, divided into two groups: 1) superficial extension (SE) group (n=10); and 2) non-SE group (n=32).

Results Only serum levels of alkaline phosphatase tended to be greater in the non-SE group than in the SE group. In terms of macroscopic growth of the main tumor, papillary type was more common in the SE group than in the non-SE group, whereas nodular type was dominant in the non-SE group. Prevalence of cancer-positive findings at the cut-end of the bile duct was higher in the SE group. Portal vein invasion was not observed in the SE group and prevalence of regional lymph node metastasis was significantly greater in the non-SE group than in the SE group. No patients died of cancer in the SE group, which tended to show better survival than the non-SE group.

Conclusion The present results suggest that good prognosis may be achieved in BDC patients with SE when complete resection is accomplished.

Introduction

With improvements in early diagnosis from laboratory and imaging examinations, the number of cases with resectable bile duct carcinoma (BDC) has increased and patient survival has improved in recent years (1,2). In some BDC patients, carcinoma spreads from the main tumor lesion along the bile duct epithelium with wide extension (3, 4). This tumor extension represents a serious obstacle to obtaining curative surgical resection when the carcinoma remains at the cut end of the bile duct (5). Remnant carcinoma would be associated with local tumor recurrence after operation. Despite advances in diagnostic imaging technology such as direct cholangiography, multi-detector computed tomography (CT) and magnetic resonance cholangiography (MRC), accurately detecting superficial extension of BDC remains difficult (1,6,7). Although only intra-luminal biopsy allows preoperative diagnosis of tumor extension, this diagnostic modality cannot be always accomplished in all preoperative BDC patients (8). The pathogenesis or clinicopathological characteristics of such a tumor may differ from BDC without wide epithelial extensions (9, 10). The characteristics of BDC with superficial extension must be determined to predict this possibility preoperatively. In the present study, to clarify specific characteristics of BDC with superficial extension of epithelium in the bile duct in a preliminary study, we examined clinicopathological features and patient outcomes in 42 BDC patients with or without superficial extension who underwent surgical resection.

Patients and methods

Subjects comprised 42 consecutive patients (29 men, 13 women) with extrahepatic BDC who underwent surgical resection in the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS), Japan, between January 1994 and April 2008. The present study defined BDC with superficial extension of epithelium in the bile duct >20 mm from the main tumor as superficial extension (SE) (Fig. 1) (11). The SE group comprised 10 of the 42 patients (24%). Tumors were preoperatively assessed by CT, MRC and cholangiography. Surgical resections were performed en bloc based on the preoperative imaging diagnosis and lymph node dissection was performed on the hepatoduodenal ligament, surrounding the pancreas head and para-aortic lesions. All tumors were resected without macroscopic exposure of the amputated section. We referred to The Classification of Biliary Tract Carcinoma to evaluate clinicopathological findings in biliary carcinomas (12). The study design was approved by the Ethics Committee of NUGSBS and a signed consent form was obtained from each patient before the procedure.

Continuous data were expressed as mean \pm standard deviation. Data from different groups were compared using one-way analysis of variance (ANOVA) followed by Student's t-test. Categorical data were analyzed using the χ^2 test or Fisher's exact test. Overall survival rates were calculated according to the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test. A two-tailed value of $P < 0.05$ was considered significant. Statistical analyses were performed using SAS software (Statistical Analysis System, Cary, NC).

Results

Mean age of all BDC patients at the time of surgery was 66 ± 11 years (range, 30-79 years). Table 1 shows a comparison of patient demographics between non-SE and SE groups. Age, sex, prevalence of preoperative jaundice, history of biliary diseases such as extrahepatic bile duct stones, gallstones, or pancreaticobiliary maljunction, and location of tumor were similar between groups. Preoperative tumor markers and liver functions were similar between groups, but only alkaline phosphatase level tended to be greater in the non-SE group than in the SE group (not significant). Table 2 shows the macroscopic or histological findings from each group. In terms of macroscopic growth type of the main tumor, papillary type was more common in the SE group than in the non-SE group.

Conversely, nodular type was predominant in the non-SE group. Prevalence of cancer-positive findings at the cut-end of the bile duct was greater in the SE group than in the non-SE group. Portal vein invasion was not observed in the SE group, although this finding was observed in 39% of the non-SE group. Prevalence of regional lymph node metastasis was higher in the non-SE group than in the SE group. Curability and postoperative recurrence rate did not differ between groups. Figure 2 shows patient outcomes after surgery. None of the patients in the SE group died of cancer, and this group tended to display better survival than the non-SE group. Three- and 5-year survival rates in the SE group were both 48%.

Discussion

Carcinomas of the extrahepatic bile duct spread longitudinally either intramurally or superficially along the bile duct (10,11,13-15). Superficial spread may be associated with macroscopic appearance of the main tumor, which influences curability in cases of surgical resection (10). This type of infiltration cannot be easily detected by conventional radiological examinations and may be detected only by cholangioscopy (13). The clinical significance of this infiltration has not been fully clarified. Examination of the characteristics or factors associated with BDC with superficial extension must therefore be determined. Our previous study identified spread beyond 20 mm as superficial extension, and this definition was applied in the present study (11).

The carcinogenesis of BDC may be influenced by initial liver diseases such as a biliary stone, pancreaticobiliary maljunction or chronic hepatitis (16-19). However, in the present result, these factors were not associated with occurrence of SE. In some cases, preoperative biliary drainage was performed to improve jaundice and we suspected this may have accelerated SE. However, no relationship with SE was observed. We also examined some parameters of preoperative hepatic functions in both groups to predict SE preoperatively. However, specific findings to predict SE were not observed and only alkaline phosphatase level tended to be higher in the non-SE group, which might not be useful to define SE. SE might not be related to tumor location (20) and we encountered ampullary carcinoma widely and superficially extending to the hilar bile ducts. SE must therefore be considered in carcinomas of any sites of the bile duct.

Macroscopic findings have been considered the most important factor associated with SE. In particular, papillary carcinomas often show superficial extension of the bile duct (10,14). As in those reports, SE was significantly more frequent with the papillary type and also in the flat type of bile duct in our series. Papillary carcinomas can be preoperatively diagnosed by various imaging modalities (1,6,7). In cases of papillary carcinomas in the bile duct, the frequent possibility of SE should be carefully considered during operation, even if intraluminal appearance of the bile duct is observed as normal in the surgical margins of the bile duct. Okamoto *et al.* examined the

characteristics of papillary carcinomas, with SE in 53%, multicentric carcinogenesis, pancreatobiliary maljunction and a survival benefit for clearance by surgical resection (10).

Although precise diagnosis of the range of tumor extension might be difficult in this type of lesion, the longer survival would be expected with only aggressive surgery.

Histological findings of the carcinoma represent important parameters to define malignant behaviors in bile duct carcinomas (21). Carcinomas with SE showed no portal infiltration and less lymph node metastasis compared to those without SE, which may indicate the potential for lower malignant activity in BDC with SE. Contrary to histological results, incidences of tumor recurrence were not significantly different between groups and previous reports have not clarified tumor recurrence and patterns of tumor spread at this stage. Sasaki *et al.* and Nakanishi *et al.* reported cases of local recurrence with a long disease-free period by follow-up after initial resection. Growth seems slow in carcinomas with SE and, although care must be taken regarding tumor recurrence for a long period of >10 years (22, 23). At this stage, extensive curative resection was necessary for BDCs either with SE or without SE regardless of poorer prognostic influences, as surgical resection was the only hope for long-term survival in BDC patients (2).

Survival for BDCs with SE would be expected to be good given the histological characteristics (10). As expected, all cases in the SE group might remain alive as of the time of writing despite tumor recurrence in some cases, with significantly better survival than patients without SE in the present study. Therefore, in cases of superficial tumor extension remaining at the surgical margin of the bile duct, rapid tumor development would not be expected after surgery and additional adjuvant treatment can be considered later. However, the number of patients in the present study was relatively small and sufficiently significant results could not be obtained at this stage. To clarify these provisional results, further examination of a larger number of patients in a multi-center analysis is necessary in the future. We have attempted photodynamic therapy to control such local remnants of carcinoma in recent years (24).

In conclusion, we have provided a preliminary report of 10 patients with BDC showing SE along the bile duct epithelium, and compared findings for these patients to those from 32 patients without SE. Papillary- or flat-type BDC tended to show SE. Portal invasion or node metastasis might be rare in the SE group and good patient prognosis could be observed in this group. Careful follow-up for a long period is necessary in patients with BDC and SE, due to the characteristic slow growth of this type of tumor. Adequate timing of treatment at tumor recurrence may provide good outcomes, although the patient cohort was limited in the present study.

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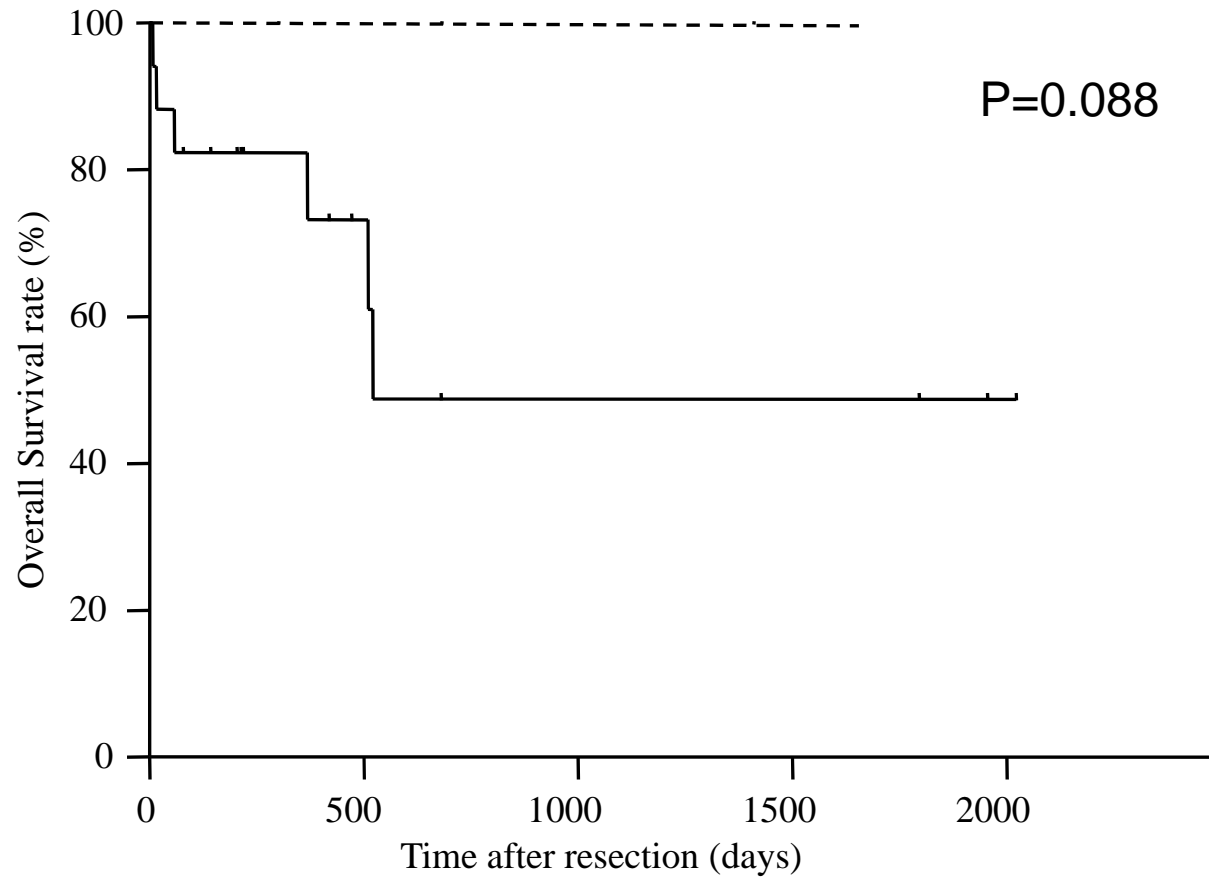
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FIGURE LEGENDS

Figure 1. Overall survival of BDC patients with or without superficial extension. Solid line, non-SE group; dotted line, SE group.

Fig 1



Survival rates	1 year	3 year	5 year
Non-SE group	82	48	48
SE-group	100	100	-

Table 1. Comparison of demographic and clinicopathological findings between BDC patients with and without SE

Factor	Non-SE group (n=32)	SE group(n=10)	p
Age (years)	66±11 (41-79)	66±15 (30-77)	0.97
Sex (male/female)	22/10	7/3	0.53
Preoperative jaundice (no/yes)	25/7	6/4	0.14
Preoperative biliary drainage(no/yes)	26/6	5/5	0.12
History of biliary diseases (no/yes)	3/29	2/8	0.57
Pancreatobiliary maljunction (no/yes)	30/2	9/1	1.0
Location of BDC			
Hilar/Upper/Middle/Lower	21/1/5/5	3/1/2/3	0.16
Preoperative serum level			
Carcinoembryonic antigen	4.2±6.2	3.5±2.9	0.74
CA19-9	149±208	156±258	0.99
Total bilirubin	2.3±1.9	2.3±1.6	0.59
Alkaline phosphatase	788±557	450±238	0.086
Macroscopic main tumor size (mm)	29.3±13.3	28.6±10.5	0.93
Macroscopic type (papillary/nodular/flat)	1/22/9	3/3/4	0.017
Finding of bile duct at cut-end (thin/thick, hard)	20/12	8/2	0.16
Cancer-positive in BD at cut-end (no/yes)	29/3	4/6	0.004
Histological differentiation			
Papillary/Well/Moderate/Poor/Adenosquamous	2/9/12/7/2	1/4/2/3/0	0.73
Venous infiltration (no/yes)	7/25	5/5	0.228
Perineural infiltration (no/yes)	9/23	5/5	0.17
Portal invasion (no/yes)	23/9	10/0	0.086
Depth of tumor invasion* (fm/ss/se/si)	2/16/3/11	2/6/0/2	0.38
Lymph node metastasis (no/yes)	13/19	8/2	0.038
Curability (A/B/C [†])	7/14/11	2/2/6	0.30
Local recurrence (no/yes)	29/3	9/1	1.0
Distant recurrence (no/yes)	26/6	8/2	1.0

*fm, invasion limited to the fibromuscular layer; ss, invasion limited to the subserosal layer; se, invasion of the serosal surface; si, invasion beyond the serosal layer and into other organs or structures. [†]Curability A showed complete resection and C showed incomplete resection due to presence of remnant tumor (12).