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의학석사 학위논문

A multicenter study for clinical impact of pancreatic invasion in T1 distal bile duct cancer (DBC) and prognostic factors associated with long-term survival

원위부 담도암의 T1 병기에서의 췌장 침범에 대한 임상적 의미 및 장기 생존율과 연관된 예후인자 분석을 위한 국내 다기관 연구

울 산 대 학 교 대 학 원
의 학 과
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지 도 교 수　　황 대 욱

이 논문을 의학석사 학위 논문으로 제출함

2023년 8월

울 산 대 학 교 대 학 원
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2023년 8월

Abstract

Introduction: Distal bile duct cancer (DBC) staging is revised from adjacent organ invasion of AJCC 7th edition to depth of invasion of AJCC 8th edition. Adequacy of recent staging system of DBC is controversial in that the invasion of organ around the distal bile duct is clinically meaningful and has an impact on prognosis of DBC. This study aimed to evaluate the pancreatic invasion of DBC in T1 stage and analyze the prognostic factors associated with long-term survival of DBC with pT1.

Methods: This study is a multicenter retrospective analysis from 6 tertiary center in Korea. We identified patients with DBC who underwent pancreaticoduodenectomy with pT1 stage of AJCC 8th edition in 6 centers from 2009 to 2019. The 5-year recurrence-free survival (RFS) and overall survival (OS) were analyzed and multivariate analysis for prognosis of pT1 DBC was performed.

Results: 287 patients were included in this study. 5-year OS of DBC with pT1 was 63.9% (95% confidence interval [CI]: 0.582-0.702) and 5-year RFS of that was 56.2% (95% CI: 0.502-0.629). There was no significant difference according to pancreatic invasion in 5-year OS (without pancreatic invasion group, 69.9% vs. with pancreatic invasion group, 54.1, p=0.25) and 5-year RFS (without pancreatic invasion group, 56.3% vs. with pancreatic invasion group, 55.4%, p=0.97). In multivariate analysis, the factors associated with OS was male (hazard ratio [HR]: 1.92, CI 1.23-3.01, p=0.004), age (HR: 1.03, CI 1.01-1.06, p=0.007), invasion of ampulla of Vater (HR: 0.49, CI 0.27-0.90, p=0.20), lymphovascular invasion (HR: 2.15, CI 1.43-3.23, p<0.001), R1 resection (HR: 2.09, CI 1.07-4.10, p=0.031) and N stage (N1; HR: 2.09 CI 1.28-3.42, p=0.003, N2; HR: 4.94, CI 2.14-11.4, p<0.001). Among the factors for OS, male (HR: 1.87, CI 1.20-2.92, p=0.005), invasion of ampulla of Vater (HR: 0.50, CI 0.29-0.87, p=0.015), lymphovascular invasion (HR: 2.07, CI 1.39-3.06, p<0.001) and N1 stage (HR: 2.23,

CI 1.39-3.56, $p<0.001$) were also significantly associated with RFS.

Conclusion: The impact of pancreatic involvement on long-term prognosis in DBC with pT1 was not observed, which is in line with the depth-based system of AJCC 8th staging.

Keywords: distal bile duct cancer, pT1, pancreatic invasion, survival analysis, prognostic factor

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Introduction

Cholangiocarcinoma, or biliary tract carcinoma, refers to a variety of invasive adenocarcinomas, that develop in the intrahepatic, perihilar, or distal biliary tree[1]. Bile duct carcinomas make up 3% of all gastrointestinal malignancies globally and are more common in Eastern Asian nations including Korea, China, and Thailand[2,3]. According to statistics from 2019 nationwide cancer statistics in Korea, biliary tract cancer and gallbladder cancer was newly diagnosed in 7,300 cases every year with crude incidence rate 14.4 per 100,000, but the survival rate was the second lowest as 28.5% following pancreas cancer (13.9%)[4]. Bile duct cancer is divided based on the location of the tumor[5]. Distal bile duct cancer (DBC), or distal cholangiocarcinoma, which makes up 20% to 40% of all identified cholangiocarcinomas, is a tumor that develops in the common bile duct below the junction of the cystic duct and above the ampulla of Vater[6]. DBC accounts for 11-20% of periampullary tumor which of standard treatment is pancreaticoduodenectomy (PD)[7,8]. Resectability at presentation of DBC is low as 35%, and even after curative surgery, 5-year overall survival remains at 40% with median overall survival ranging from 35-48 months[9-13].

The staging of DBC is divided according to the American Joint Committee on Cancer (AJCC) cancer staging. From the 7th to the 8th edition of the AJCC, published in 2016, the T staging system of DBC has been completely revised[14,15]. The AJCC 7th edition used a anatomic layer-based approach, which was criticized for vague description, such as “confined to the bile duct” and “beyond the wall of the bile duct”, resulting in interobserver variation and inaccurate classification for predicting survival of patients with DBC[16-20]. To overcome these problems, AJCC 8th edition classified T stage based on depth-based approach measuring the depth of invasion and reported to evaluate the prognosis better than previous edition[16,17,21-23].

Despite this change, studies have reported that organ invasion in the previous 7th

edition system still has an impact on prognosis[22,24]. Especially in clinical practice, tumors with a depth of less than 5 mm but with pancreatic invasion were downstaged from T3 to T1 from the AJCC 7th edition to the 8th edition. In these cases, it is not yet known whether surrounding organ involvement is still a prognostic factor in patients with T1 stage. Therefore, this study aims to analyze whether adjacent organ involvement, which was a criterion in the previous 7th edition of T staging, affects prognosis in patients with DBC who have undergone radical surgery and have a T1 stage according to the AJCC 8th edition. In addition, we would like to explore what other factors affect prognosis in T1 stage of DBC and what factors are necessary for staging.

2 Materials and methods

2.1 Study population

To calculate the number of subjects, we used the 5-year survival of stage I (T1N0M0) as 69.3% based on the AJCC 8th edition and stage IIA (T3N0M0) as 53.5% as based on one of Korean tertiary center[16,22]. With an alpha of 0.05, a beta of 0.2, and a survival improvement of 0.15, a total of 219 patients were calculated to be required. The study was conducted as a multicenter retrospective design to ensure adequate participant recruitment and a total six tertiary center (Asan Medical Center; AMC, Samsung Medical Center; SMC, Seoul National University Hospital; SNUH, Seoul National University Bundang Hospital; SNUBH, Yonsei University Health system; YUHS, National Cancer Center; NCC) in Korea was participated in this study. The Institutional Review Board of Asan Medical Center (registration no: 2022-1658) approved this study.

Patients with T1 stage of AJCC 8th of DBC who underwent pancreaticoduodenectomy (PD) from January 2009 to December 2019 were identified. In addition, only patients with a cancer focus in the intrapancreatic bile duct were included to confirm pancreatic invasion. To evaluate both 7th and 8th edition T staging, patients with pathologic reports on depth of invasion and adjacent organ invasion were included. Patients who underwent bile duct resection (BDR) and hepatopancreaticoduodenectomy (HPD) were excluded from the study. In the case of BDR, the surgical specimen does not include pancreas and duodenum, making it difficult to properly evaluate the involvement of other organ surrounding biliary tract, and in the case of HPD, differentiation from perihilar cholangiocarcinoma is necessary and HPD itself increases surgical mortality. Patients who

underwent R2 resection and had distant metastases were also not included in the study since they are known confounding variables for oncologic outcomes.

2.2 Surgical procedure and postoperative adjuvant therapy

Standard PD (Whipple procedure), pylorus-preserving PD with preservation of the entire stomach, and pylorus-resecting PD with resection of only the pyloric ring with preservation of nearly all the stomach were done on the preference of each surgeon[25,26]. After surgery, part of patients received adjuvant therapy. Adjuvant chemotherapy was administered in various regimens such as 6 cycles of uracil-tegafur (UFT) with or without leucovorin (LV), 6 cycles of LV/5-FU, 6 or 8 cycles of gemcitabine/cisplatin, and 12 cycles of 5-FU/levofolic/cisplatin. Adjuvant chemoradiotherapy was done in combination like LF-CRT (LV/5-FU with 5400 cGy/30Fx) or CCRT-Xeloda (capecitabine with 5040 cGy/30Fx). All patients were followed up postoperatively according to their respective institutional protocols.

2.3 Clinicopathologic findings

Clinical and pathologic data were collected based on electronic medical records (EMR) system of each center. The data obtained were as follows: gender, age, American Society of Anesthesiologists (ASA) score, operation date, discharge date, operative details, survival status, recurrence, histologic subtype, differentiation, depth of invasion, invasion of adjacent organ including duodenum, ampulla of Vater, pancreas, gallbladder, cystic duct, lymphovascular invasion, perineural invasion, nodal metastasis, resection margin status, stage based on 8th AJCC cancer staging system, postoperative complication and its Clavien-Dindo

class, and adjuvant therapy. R1 resection was defined as invasion of adenocarcinoma, high grade dysplasia, or biliary intraepithelial neoplasia 3 was observed at resection margin.

2.4 Outcome

Primary outcome of the study was overall survival (OS) and recurrence-free survival (RFS) according to pancreatic invasion. OS and RFS were measured from the date of surgery to the date of the death from any cause or first recurrence, respectively. Recurrence was confirmed by radiologic imaging or histopathologic findings. Secondary outcome was survival analysis according to adjuvant therapy and prognostic factors associated with survival of DBC with pT1.

2.5 Statistical analysis

Sample size calculation and statistical analyses were carried out using R (version 4.1.1). Baseline variables of clinicopathologic data were presented as absolute number, percentage or median with interquartile range (IQR). Survival outcomes were calculated using the Kaplan–Meier method and compared using log-rank tests according to the status of pancreatic invasion, T staging of AJCC 7^{th}, and adjuvant therapy. The Cox proportional hazard regression analyses were used for multivariate analysis of factors associated with OS and RFS. Statistical significance was assumed at $p<0.05$.

3 Results

3.1 Clinicopathological characteristics of patients

A total of 287 patients were included (AMC, n = 130; SMC, n = 75; YUHS, n = 30; SNUBH, n = 22; SNUH, n = 21; NCC, n = 9) (Table 1). The majority of the patients were male (71%) and the median age was 68 years (IQR 61-74). Most patients had an ASA score of II (72%), and the median hospital stay after operation was 13 days. The most common type of surgery was pylorus-preserving pancreaticoduodenectomy (PPPD) (76%), and most surgeries were performed using an open approach (85%). The median time of operation was 315 minutes.

The majority of patients had adenocarcinoma (97%) with a moderate differentiation (65%). The table also provides information on the invasion of adjacent structures by DBC, including the duodenum, ampulla of Vater, pancreas, gallbladder, and cystic duct. Reclassifying to the 7th edition revealed that 21.6% of patients were in the T1 stage, 39.4% were in the T2 stage, and 39.0% were in the T3 stage. Lymphovascular and perineural invasion was present in 33% and 59% of patients, respectively. Most of the patients had an R0 resection (94%). According to the AJCC 8th edition, the M stage of all patients was M0, and the final staging was categorized as stage I, IIA, or IIIA according to the N stage (N0, or I, n = 237; N1, or IIA, n = 42; N2, or IIIA, n = 8). Postoperative complications occurred in 56% of patients, with most complications being Clavien-Dindo class II or IIIa. Adjuvant treatment was administered to 34% of patients, with 23% receiving chemotherapy and 11% receiving concurrent chemoradiotherapy.

Table 1. Clinicopathological characteristics of the study patients

Characteristics	N = 287[1]
Gender	
Female	83 (29%)
Male	204 (71%)
Age	68 (61, 74)
ASA score	
0	1 (0.3%)
I	24 (8.4%)
II	207 (72%)
III	54 (19%)
IV	1 (0.3%)
Hospital days (postoperative)	13 (10, 19)
Type of operation (1)	
PD[2]	25 (8.7%)
PPPD[2]	219 (76%)
PrPD[2]	43 (15%)
Type of operation (2)	
Open	245 (85%)
Laparoscopic	23 (8.0%)
Robotic	19 (6.6%)
Time of operation	315 (262, 370)
Histologic subtype	
Adenocarcinoma	279 (97%)
Adenosquamous carcinoma	5 (1.7%)
Intraductal papillary neoplasm	2 (0.7%)
Signet ring cell carcinoma	1 (0.3%)

Characteristics	N = 287[1]
Differentiation	
Well	48 (17%)
Moderate	182 (65%)
Poorly	50 (18%)
Undifferentiated	1 (0.4%)
Not available	6
Beyond bile duct	
Absent	62 (22%)
Present	225 (78%)
Invasion of duodenum	
Absent	271 (94%)
Present	16 (5.6%)
Invasion of ampulla of Vater	
Absent	241 (84%)
Present	46 (16%)
Invasion of pancreas	
Absent	190 (66%)
Present	97 (34%)
Invasion of gallbladder	
Absent	277 (97%)
Present	10 (3.5%)
Invasion of cystic duct	
Absent	242 (84%)
Present	45 (16%)
Lymphovascular invasion	
Absent	191 (67%)
Present	96 (33%)

Characteristics	N = 287[1]
Perineural invasion	
Absent	118 (41%)
Present	169 (59%)
Resection margin status	
R0	269 (94%)
R1	18 (6.3%)
T stage (7^{th})	
T1 (confinement to bile duct)	62 (21.6%)
T2 (beyond bile duct)	113 (39.4%)
T3 (invasion of adjacent organs)	112 (39.0%)
N stage (8^{th})	
N0	237 (83%)
N1	42 (15%)
N2	8 (2.8%)
M stage (8^{th})	
M0	287 (100%)
Stage (8^{th})	
I	237 (83%)
IIA	42 (15%)
IIIA	8 (2.8%)
Postop complication	
None	127 (44%)
Present	160 (56%)
Clavien-Dindo class of complication	
I	35 (12%)
II	57 (20%)
IIIA	45 (16%)

Characteristics	N = 287[1]
IIIB	4 (1.4%)
IVA	16 (5.6%)
IVB	2 (0.7%)
V	1 (0.3%)
Adjuvant treatment	
Not done	190 (66%)
CTx[3]	65 (23%)
CCRT[3]	32 (11%)

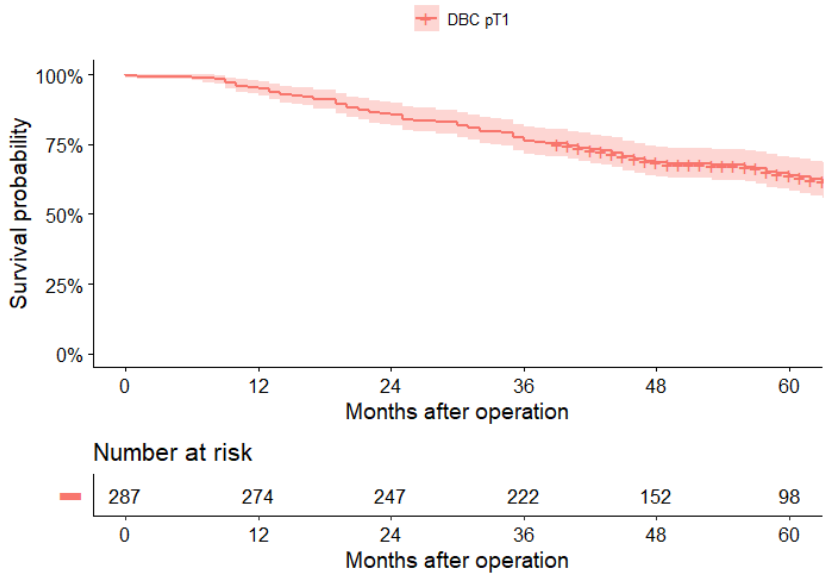
[1]n (%); Median (IQR), [2]PD, pancreaticoduodenectomy; PPPD, pylorus preserving pancreaticoduodenectomy; PrPD, pylorus resecting pancreaticoduodenectomy, [3]CTx, chemotherapy; CCRT, concurrent chemoradiotherapy

3.2 Oncological outcome : 5-year overall survival and recurrence-free survival

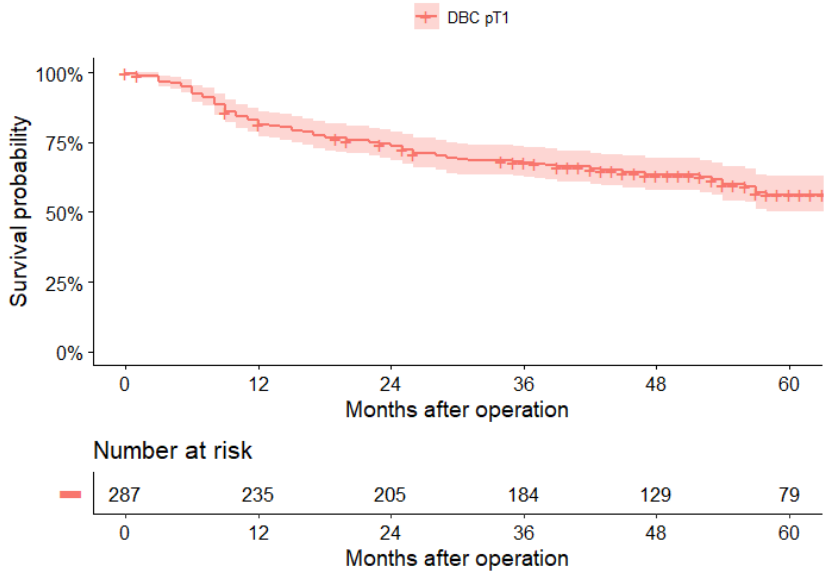
Out of 287 patients, 114 (40%) died and 118 (41%) relapsed throughout the observation period. There were 83 systemic and 54 locoregional recurrences.

The 5-year OS rate was 63.9% (95% CI: 58.2-70.2%) and the RFS rate was 56.2% (95% CI: 50.2%-62.9%) in the total patient population (Figure 1). When comparing the survival outcome between the two groups stratified by pancreatic invasion, there was no difference in 5-year OS (without, 69.9%, 95% CI: 63.4-77.2% vs. with, 54.1%, 95% CI: 44.5-65.6%; $p = 0.25$) and 5-year RFS rate (without, 56.3%, 95% CI: 48.8-65.0% vs. with, 55.4%, 95% CI: 45.9-66.8%; $p = 0.97$) (Figure 2 A, B). When the survival rate was further divided into N- and N+ groups according to the absence or presence of metastatic lymph nodes, the survival rate changed according to the status of lymph node metastasis ($p<0.0001$) (Figure 2 C, D). In N- group, the 5-year OS and RFS rate for patients without pancreatic invasion were 74.8% (95% CI: 67.9-82.4%) and 61.2% (95% CI: 53.2-70.4%), and those for patients with pancreatic invasion were 61.1% (95% CI: 50.8-73.6%) and 62.8% (95% CI: 52.6-74.9%). The 5-year OS and RFS of N+ group were significantly lower in that those without pancreatic invasion were 46.7% (95% CI: 32.2-67.7%) and 26.4% (95% CI: 10.5%-66.5%), and those with pancreatic invasion were 22.5% (95% CI: 8.8%-57.7%) and 19.3 (95% CI: 6.3-58.5%).

Figure 1. Kaplan-Meier survival graph of oncological outcomes of total patients. A. OS B. RFS



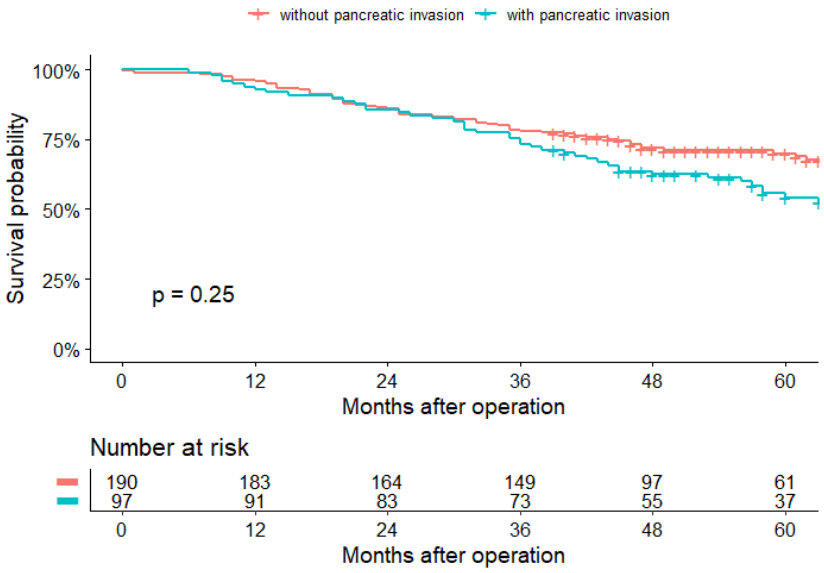
A.



B.

Figure 2. Kaplan-Meier survival graph of oncological outcomes according to the invasion of pancreas. A, B. OS and RFS of patients (total); C, D. OS and RFS of patients with the absence or presence of lymph node metastases (N- or N+)

A.



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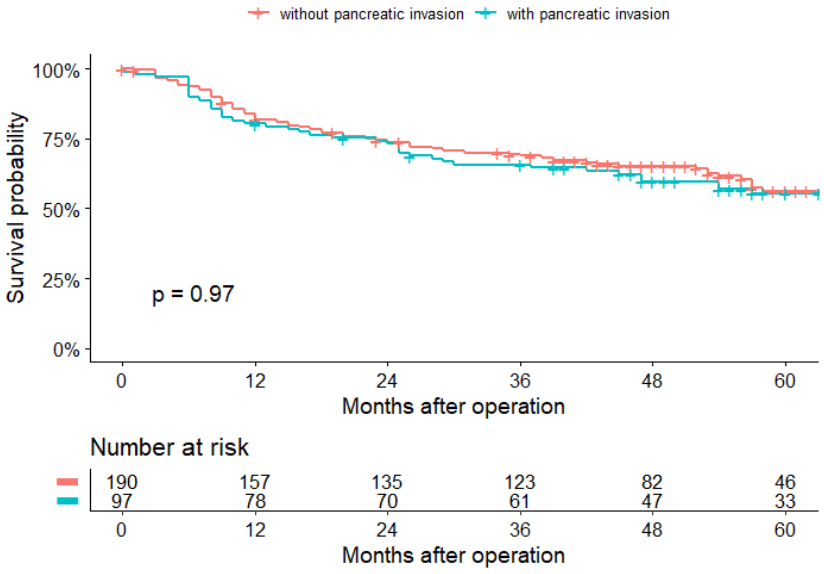
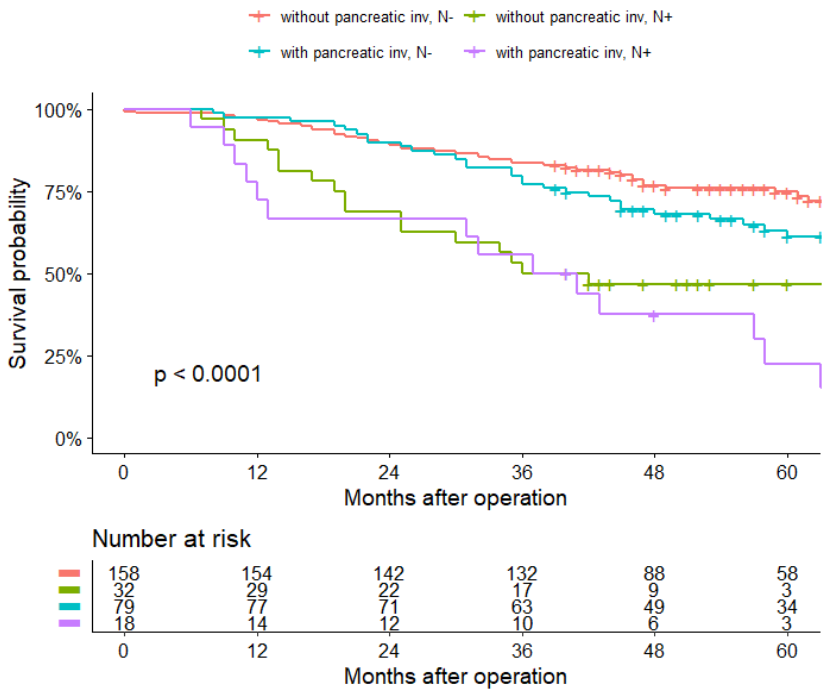
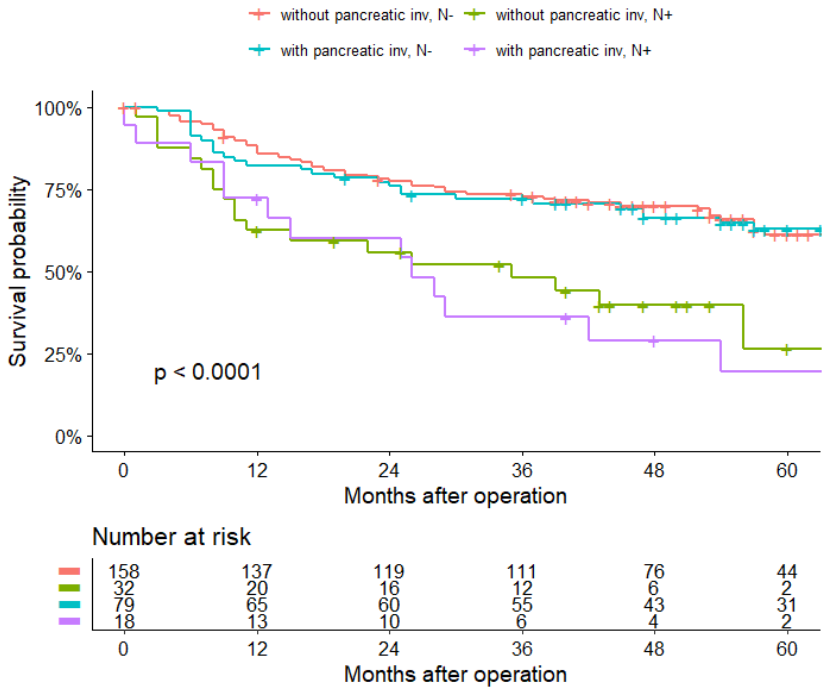


C.

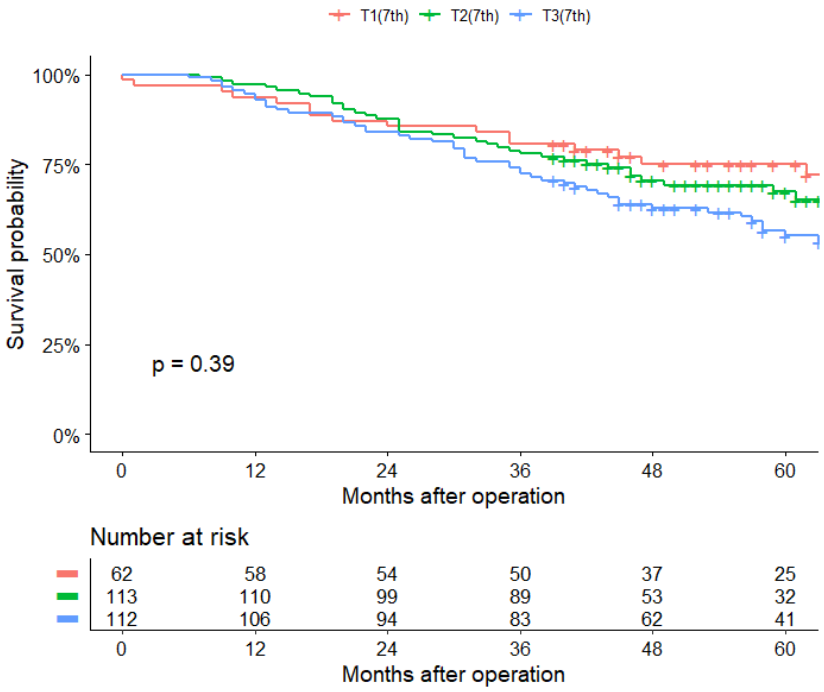

without pancreatic inv, N-
without pancreatic inv, N+
with pancreatic inv, N-
with pancreatic inv, N+
Survival probability
100%
75%
50%
25%
0%
p < 0.0001
0
12
24
36
48
60
Months after operation
Number at risk
158 154 142 132 88 58
32 29 22 17 9 3
79 77 71 63 49 34
18 14 12 10 6 3
0
12
24
36
48
60
Months after operation

D.

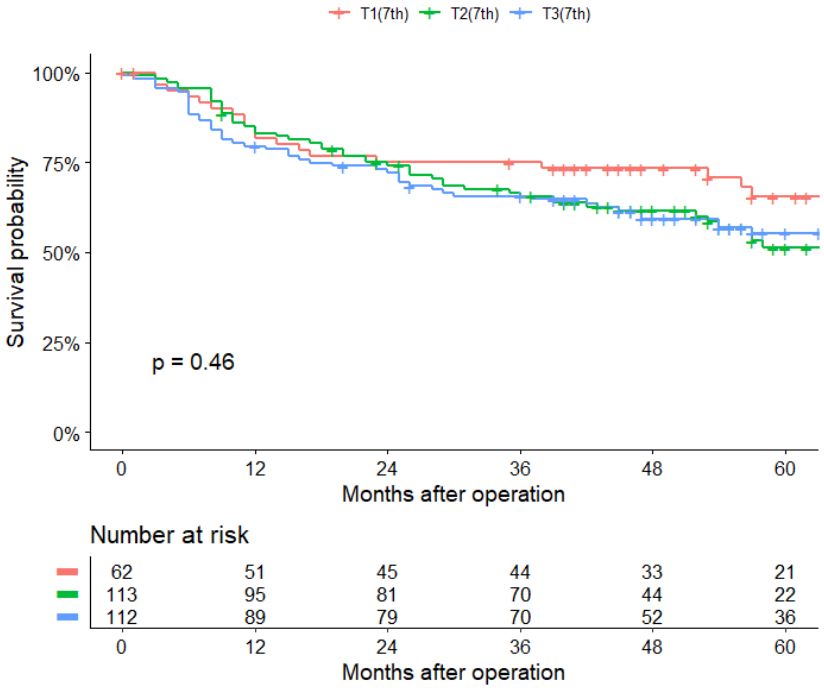

without pancreatic inv, N-
without pancreatic inv, N+
with pancreatic inv, N-
with pancreatic inv, N+
Survival probability
100%
75%
50%
25%
0%
p < 0.0001
0
12
24
36
48
60
Months after operation
Number at risk
158 137 119 111 76 44
32 20 16 12 6 2
79 65 60 55 43 31
18 13 10 6 4 2
0
12
24
36
48
60
Months after operation

According to the AJCC 7th edition T staging criteria, there were 62 patients in the T1 stage, 113 patients in the T2 stage, and 112 patients in the T3 stage (Figure 3). The 5-year OS rate was 75.1% (95% CI: 64.8-86.9%), 67.3% (95% CI: 58.6-77.4%), and 55.1% (95% CI: 46.1-65.9%) for T1, T2, and T3 stage patients, respectively. Similarly, the 5-year RFS rate was 65.3% (95% CI: 53.4-79.9%), 51.3% (95% CI: 41.6-63.2%), and 55.4% (95% CI: 46.4-66.0%) for T1, T2, and T3 stage patients, respectively. There was no significant difference in the 5-year OS ($p = 0.25$) or 5-year RFS rate ($p = 0.97$) between patients based on the 7th edition T staging of the AJCC.

Figure 3. Kaplan-Meier survival graph of oncological outcomes according to T stage of AJCC 7th edition. A. OS B. RFS



A.



B.

Lastly, patients were divided into groups according to whether or not they received postoperative adjuvant therapy to compare prognosis. To exclude lymph node metastasis as a confounder, only 237 patients with T1N0 stage (final stage I) were included in subgroup survival analysis, with 173 patients receiving no adjuvant therapy, 45 receiving adjuvant chemotherapy, and 19 receiving adjuvant chemoradiotherapy (Figure 4 A, B). The 5-year OS rate for the no adjuvant group was 70% (95% CI: 64.1-78.5%), while it was 64.5% (95% CI: 50.7-82.1%) and 73.7% (95% CI: 56.3-96.4%) for the CTx and CCRT groups, respectively. The corresponding 5-year RFS rates for the no adj group, CTx group, and CCRT group were 62.2% (95% CI: 54.9-70.5%), 58.8% (95% CI: 44.5-77.8%), and 66.3% (95% CI: 47.3-92.8%), respectively. There was no significant difference in the 5-year OS ($p = 0.79$) or 5-year RFS rate ($p = 0.95$) between 3 groups categorized by adjuvant therapy.

Of the 97 patients with pancreatic involvement, 23 (24%) received adjuvant chemotherapy and 12 (12%) received adjuvant CCRT. There was no difference in the proportion of patients receiving adjuvant therapy compared to patients without pancreatic involvement (Table 2). A subgroup analysis was performed to determine if there was a difference in survival with adjuvant therapy in patients with pancreatic invasion, and no significant difference was observed (Figure 4 C, D). The 5-year OS rate for the no adjuvant, CTx, CCRT group was 56.1% (95% CI: 44.5-70.6%), 50.7% (95% CI: 32.4-79.1%) and 50% (95% CI: 28.4-87.9%), respectively ($p = 0.89$). RFS rates at 5 years were, respectively, 57.5% (95% CI: 46.0-71.9%), 57.2% (95% CI: 38.9-83.8%), and 40.0% (95% CI: 19.6-81.8%) for the no adj, CTx, and CCRT groups ($p = 0.66$).

Table 2. Adjuvant treatment according to invasion of pancreatic invasion

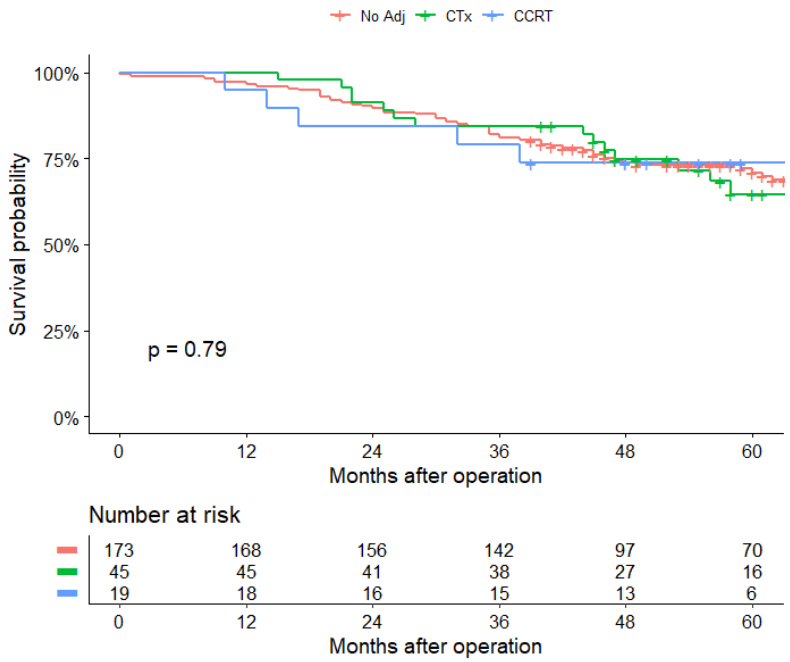
Characteristic	Pancreatic invasion -, N = 190[1]	Pancreatic invasion +, N = 97[1]	p-value[2]
Adjuvant treatment			0.8
Not done	128 (67%)	62 (64%)	
CTx	42 (22%)	23 (24%)	
CCRT	20 (11%)	12 (12%)	

[1]n (%); Median (IQR)

In patients with T3 by AJCC 7th edition to include invasion of pancreas, duodenum, gallbladder and other adjacent organs, adjuvant therapy did not improve survival outcomes (OS, p = 0.68; RFS, p = 0.82) (Figure 4 E, F). In the no adjuvant, CTx, and CCRT groups, the 5-year OS rates were 57.1% (95% CI: 45.9-70.9%), 53.5% (95% CI: 36.6-78.1%), and 48.6% (95% CI: 29.0-81.4%), and the 5-yr RFS rates were 58.6% (95% CI: 47.3-73.0%), 53.2% (95% CI: 36.9-76.6%), and 43.3% (95% CI: 22.9-81.7%), respectively.

Figure 4. Kaplan-Meier survival graph of oncological outcomes according to the adjuvant therapy A, B. OS and RFS of patients with T1N0 stage (AJCC 8th stage I); C, D. OS and RFS of patients with pancreatic invasion; E, F. OS and RFS of patients with T3 stage of AJCC 7th

A.



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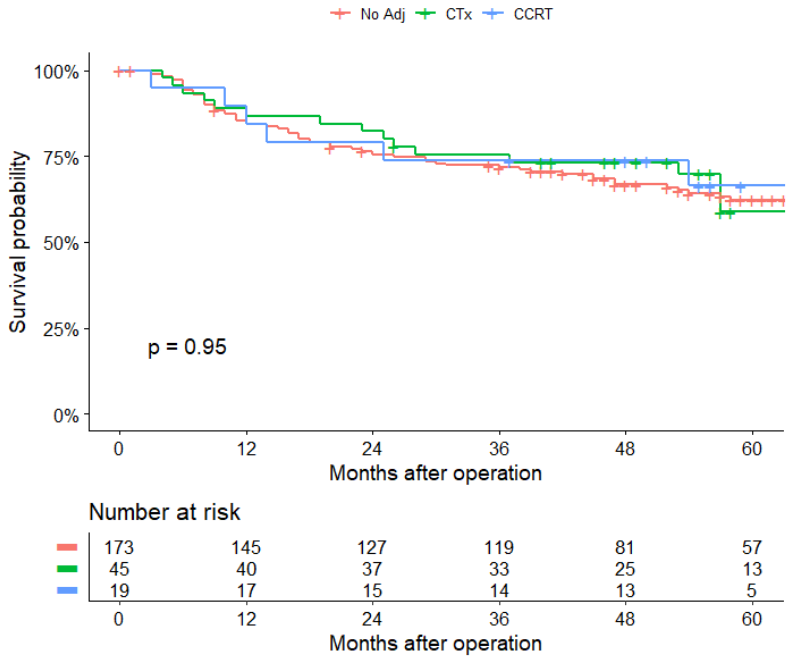
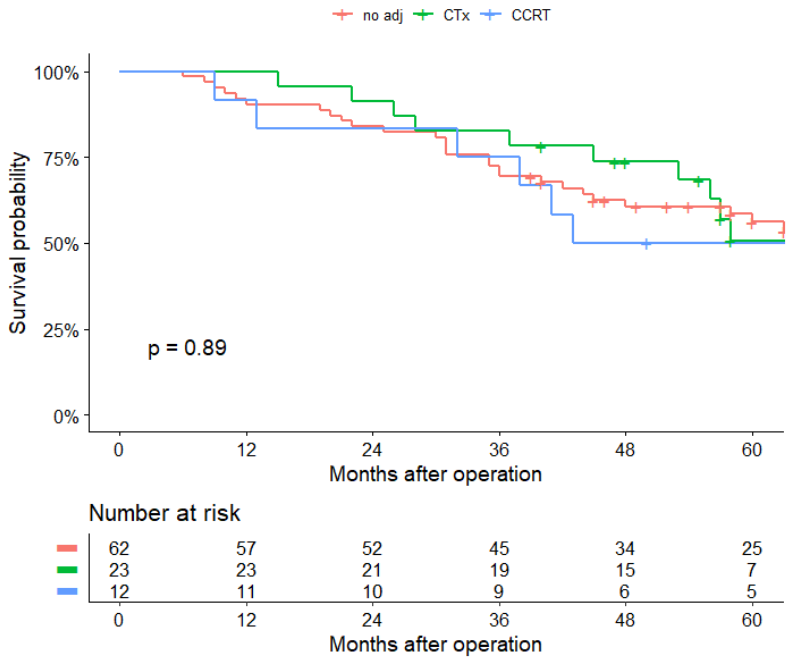


C.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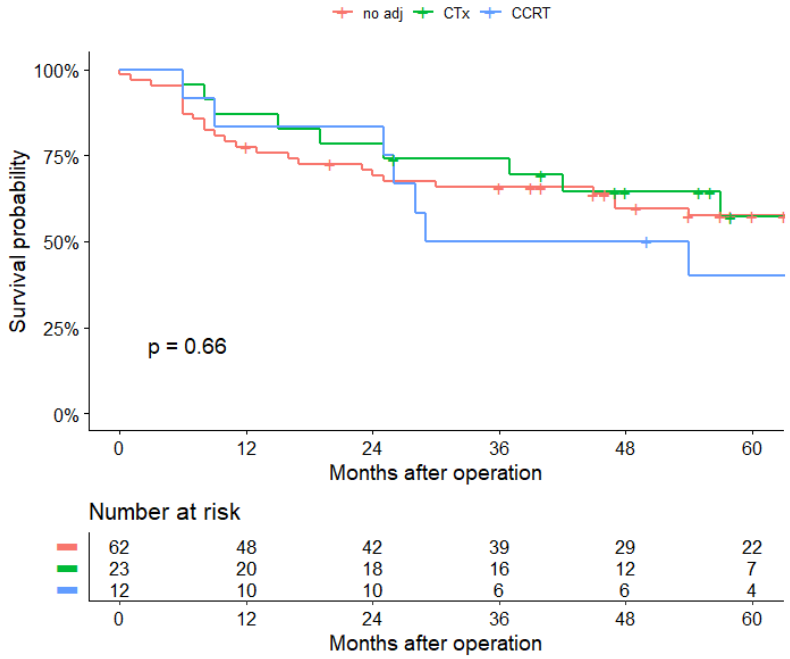
CTx
CCRT
100%
75%
50%
25%
0%
Survival probability
p = 0.89
0
12
24
36
48
60
Months after operation
Number at risk
62 57 52 45 34 25
23 23 21 19 15 7
12 11 10 9 6 5
0
12
24
36
48
60
Months after operation

D.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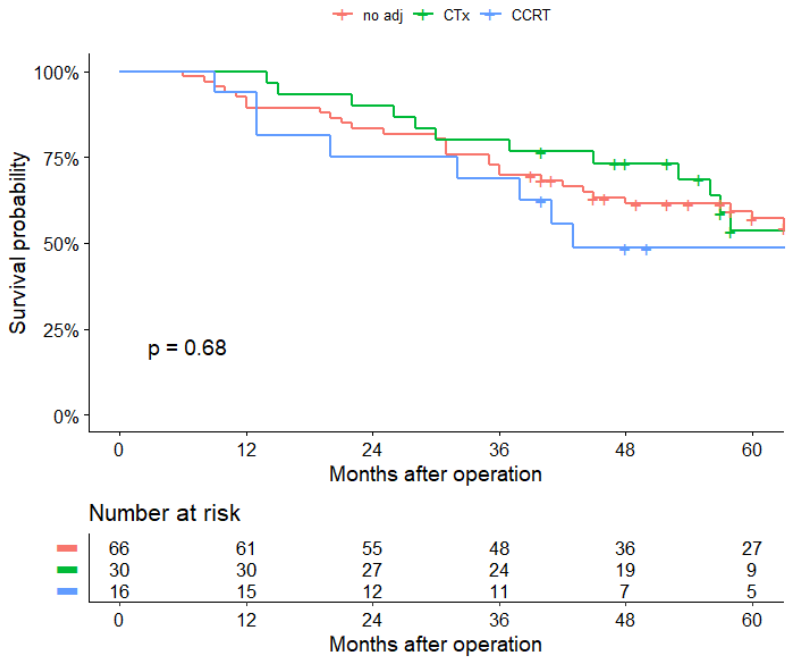
CCRT
100%
75%
50%
25%
0%
Survival probability
p = 0.66
0
12
24
36
48
60
Months after operation
Number at risk
62 48 42 39 29 22
23 20 18 16 12 7
12 10 10 6 6 4
0
12
24
36
48
60
Months after operation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CTx
CCRT
100%
75%
50%
25%
0%
Survival probability
p = 0.68
0
12
24
36
48
60
Months after operation
Number at risk
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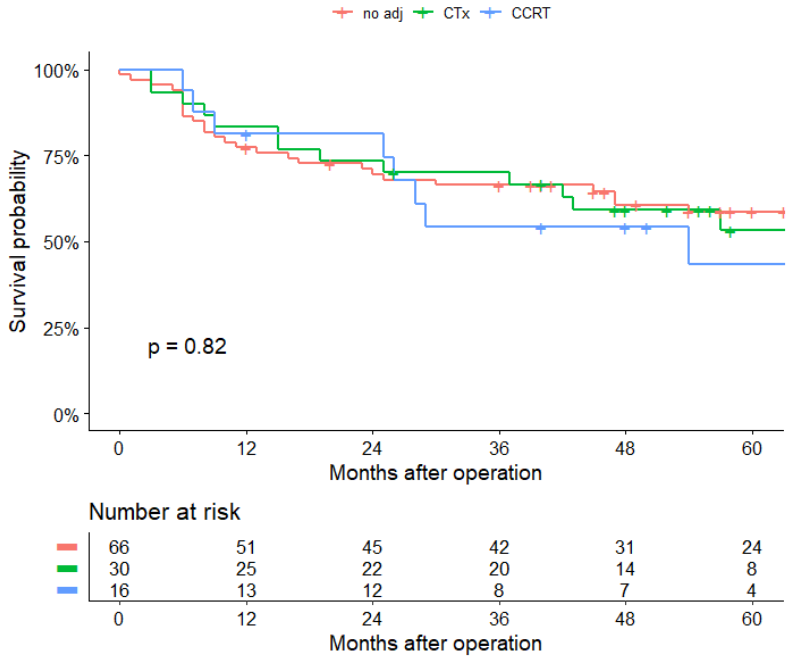
30 30 27 24 19 9
16 15 12 11 7 5
0
12
24
36
48
60
Months after operation

E.


no adj
CTx
CCRT
100%
75%
50%
25%
0%
Survival probability
p = 0.82
0
12
24
36
48
60
Months after operation
Number at risk
66 51 45 42 31 24
30 25 22 20 14 8
16 13 12 8 7 4
0
12
24
36
48
60
Months after operation

F.

3.3 Risk factors associated with overall survival and recurrence-free survival

In univariate analysis, risk factors associated with OS were male gender (HR: 1.62, p = 0.031), age (HR: 1.03, p = 0.025), poorly differentiation (HR: 2.30, p = 0.005), lymphovascular invasion (HR: 2.79, p<0.001), and N stage (N1, HR: 2.53, p<0.001; N2, HR: 5.24, p<0.001) (Table 3) . In multivariate analysis, male gender (HR: 1.92, 95% CI: 1.23-3.01, p = 0.004), age (HR: 1.03, 95% CI: 1.01-1.06, p = 0.007), lymphovascular invasion (HR: 2.15, 95% CI: 1.43-3.23, p<0.001), R1 resection (HR: 2.09, 95% CI: 1.07-4.10, p = 0.031), and N stage (N1, HR: 2.09, 95% CI: 1.28-3.42, p = 0.003; N2, HR: 4.94, 95% CI: 2.14-11.4, p<0.001) were associated with OS. Invasion of ampulla of Vater was the only factor that lower HR (HR: 0.49, 95% CI: 0.27-0.90, p = 0.020). Invasion of duodenum, pancreas, and GB, which were all classed as T3 in the 7th edition staging, did not show any significant p values in either univariate or multivariate analyses.

Table 3. Risk factors associated with overall survival

	Univariate analysis			Multivariate analysis		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
Gender						
Female	—	—		—	—	
Male	1.62	1.04, 2.51	0.031	1.92	1.23, 3.01	0.004
Age	1.03	1.00, 1.05	0.025	1.03	1.01, 1.06	0.007
Hospital days	1.01	1.00, 1.02	0.083			
Type of operation (1)						
PD	—	—				
PPPD	0.73	0.40, 1.34	0.3			
PrPD	0.67	0.32, 1.44	0.3			
Type of operation (2)						
Open	—	—				
Laparoscopic	1.90	0.77, 4.67	0.2			
Robotic	0.45	0.09, 2.31	0.3			
Time of operation	1.00	1.00, 1.00	0.4			
Pathology						
Adenocarcinoma	—	—				
Adenosquamous carcinoma	1.04	0.26, 4.19	>0.9			
Intraductal papillary neoplasm	3.03	0.42, 21.8	0.3			
Signet ring cell carcinoma	0.00	0.00, Inf	>0.9			
Differentiation						
Well	—	—				
Moderate	1.05	0.63, 1.76	0.8			
Poorly	2.30	1.28, 4.12	0.005			

	Univariate analysis			Multivariate analysis		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
Undifferentiated	0.00	0.00, Inf	>0.9			
Beyond bile duct						
Absent	—	—				
Present	1.35	0.83, 2.18	0.2			
Invasion of duodenum						
Absent	—	—				
Present	1.50	0.70, 3.23	0.3			
Invasion of ampulla of Vater						
Absent	—	—		—	—	
Present	0.59	0.33, 1.06	0.076	0.49	0.27, 0.90	0.020
Invasion of pancreas						
Absent	—	—				
Present	1.25	0.85, 1.82	0.3			
Invasion of gallbladder						
Absent	—	—				
Present	0.84	0.27, 2.66	0.8			
Invasion of cystic duct						
Absent	—	—				
Present	1.51	0.94, 2.44	0.088			
Lymphovascular invasion						
Absent	—	—		—	—	
Present	2.79	1.92, 4.04	<0.001	2.15	1.43, 3.23	<0.001
Perineural invasion						

	Univariate analysis			Multivariate analysis		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
Absent	—	—		—	—	
Present	1.43	0.97, 2.12	0.070	1.39	0.92, 2.09	0.11
Resection status						
R0	—	—		—	—	
R1	1.75	0.91, 3.36	0.091	2.09	1.07, 4.10	0.031
N stage						
N0	—	—		—	—	
N1	2.53	1.60, 4.00	<0.001	2.09	1.28, 3.42	0.003
N2	5.24	2.40, 11.5	<0.001	4.94	2.14, 11.4	<0.001
Postop complication						
None	—	—				
Present	1.10	0.76, 1.59	0.6			
Adjuvant treatment						
Not done	—	—				
CTx	0.89	0.56, 1.42	0.6			
CCRT	1.28	0.72, 2.26	0.4			

[1]HR = Hazard Ratio, CI = Confidence Interval

Both univariate and multivariate analyses of risk factors for RFS were performed (Table 4). Male gender (HR: 1.65, p = 0.024), poorly differentiation (HR: 2.05, p = 0.020), lymphovascular invasion (HR: 2.42, p<0.001), and N stage (N1, HR: 2.69, p<0.001; N2, HR: 2.60, p = 0.039) were associated with RFS in univariate analysis. After multivariate analysis, the only variables still contributing to RFS were male gender (HR: 1.87, 95% CI: 1.20-2.92, p = 0.005), lymphovascular invasion (HR: 2.07, 95% CI: 1.39-3.06, p<0.001), and N1 stage (HR: 2.23, 95% CI: 1.39-3.56, p<0.001). As in OS, multivariate analysis revealed that ampulla of Vater invasion was related to reduced HR in RFS (HR: 0.50, 95% CI: 0.29-0.87, p = 0.015). The factors that were the basis for the 7th edition staging such as beyond bile duct and invasion of adjacent organs were not found to be significant risk factors for RFS.

Table 4. Risk factors associated with recurrence-free survival

	Univariate analysis			Multivariate analysis		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
Gender						
Female	—	—		—	—	
Male	1.65	1.07, 2.55	0.024	1.87	1.20, 2.92	0.005
Age	0.99	0.97, 1.01	0.5			
Hospital days	1.00	0.99, 1.02	0.8			
Type of operation (1)						
PD	—	—				
PPPD	1.05	0.55, 2.01	0.9			
PrPD	0.87	0.39, 1.93	0.7			
Type of operation (2)						
Open	—	—				
Laparoscopic	1.26	0.61, 2.59	0.5			
Robotic	0.82	0.28, 2.37	0.7			
Time of operation	1.00	1.00, 1.00	0.4			
Pathology						
Adenocarcinoma	—	—				
Adenosquamous carcinoma	1.60	0.51, 5.04	0.4			
Intraductal papillary neoplasm	2.33	0.32, 16.7	0.4			
Signet ring cell carcinoma	0.00	0.00, Inf	>0.9			
Differentiation						
Well	—	—				

	Univariate analysis			Multivariate analysis		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
Moderate	1.17	0.70, 1.96	0.6			
Poorly	2.05	1.12, 3.75	0.020			
Undifferentiated	0.00	0.00, Inf	>0.9			
Beyond bile duct						
Absent	—	—				
Present	1.33	0.83, 2.14	0.2			
Invasion of duodenum						
Absent	—	—				
Present	1.28	0.59, 2.74	0.5			
Invasion of ampulla of Vater						
Absent	—	—		—	—	
Present	0.65	0.38, 1.11	0.12	0.50	0.29, 0.87	0.015
Invasion of pancreas						
Absent	—	—				
Present	1.01	0.69, 1.48	>0.9			
Invasion of gallbladder						
Absent	—	—				
Present	1.19	0.44, 3.22	0.7			
Invasion of cystic duct						
Absent	—	—				
Present	1.30	0.81, 2.08	0.3			
Lymphovascular invasion						
Absent	—	—		—	—	

	Univariate analysis			Multivariate analysis		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
Present	2.42	1.69, 3.48	<0.001	2.07	1.39, 3.06	<0.001
Perineural invasion						
Absent	—	—				
Present	1.27	0.87, 1.86	0.2			
Resection status						
R0	—	—				
R1	1.48	0.75, 2.91	0.3			
N stage						
N0	—	—		—	—	
N1	2.69	1.74, 4.16	<0.001	2.23	1.39, 3.56	<0.001
N2	2.60	1.05, 6.44	0.039	1.79	0.70, 4.58	0.2
Postop complication						
None	—	—				
Present	1.09	0.76, 1.57	0.6			
Adjuvant treatment						
Not done	—	—				
CTx	1.14	0.74, 1.75	0.6			
CCRT	1.28	0.73, 2.23	0.4			

[1]HR = Hazard Ratio, CI = Confidence Interval

Discussion

In cases of distal bile duct cancer with a depth of tumor invasion less than 5mm, even if they had pancreatic involvement classified as stage IIA (T3N0M0) according to the AJCC 7th edition, no significant difference in the 5-year survival rate was observed compared to cases without such involvement. Additionally, postoperative adjuvant treatment in T1 patients without lymph node metastases did not show a survival benefit. In T1 stage patients, prognostic factors for 5-year OS included male gender, advanced age, lymphovascular invasion, R1 resection, and nodal metastasis, while factors for 5-year RFS included male gender, lymphovascular invasion, and nodal metastasis. Invasion of ampulla of Vater was associated with a lower risk of survival and recurrence.

The anatomy and histology of the distal bile duct is unique. Grossly, it forms a complex anatomical structure with various organs such as pancreas and duodenum[27]. Microscopically, the bile duct wall itself lacks a well-defined muscular layer and leads to periductal tissue without clear demarcation[28]. Furthermore, the invasion of bile duct carcinoma causes a desmoplastic stromal reaction in the bile duct wall, making it difficult to determine whether it is confined within the bile duct or beyond the bile duct[21]. When peripheral pancreatic acinar cell is seen within the lower portion of bile duct wall, it may be difficult to distinguish between pancreas and bile duct wall in intrapancreatic portion[29]. To overcome the ambiguous characteristics of distal bile duct cancer, Hong et al. proposed the measurement of depth of invasion (DOI) from the basal lamina of the adjacent normal epithelium to the most deeply advanced tumor cells with cut-off values of 5 and 12mm[30]. Moon and Aoyama et al. suggested another way to measure DOI defined as the maximal vertical distance of the invasive cancer component in patients without clear visualization of basal lamina due to fibrosis evoked by cancer infiltration, associated cholangitis and catheter placement for biliary drainage,

whose DOI cannot be measured[21,31]. Park et al. measured the DOI as the distance from the imaginary curved line, supposed to be a transition zone when tracing from adjacent normal tissue to the deepest invasive front[32]. Despite these differences in metrics, DOI has been validated to correlate well with prognosis[16,17,21-23,28,30-32].

Even after the change to the 8th edition, there are researches reporting that adjacent organ invasion still affects prognosis. Kang et al. demonstrated that the 8th edition predicted survival outcomes better for T1 and T2 compared to the 7th edition, but the authors explained that this was due to the small number of T1 and T2 in the study and the downstaging of 7th edition T3 patients to 8th edition T2[22]. They found that the predictive power of the 8th edition was not statistically significantly higher than the 7th edition. They also suggested that the aggressiveness of the tumor may be underestimated because the DOI alone does not reflect the overall morphologies of the tumor. Min et al. showed that patients with organ invasion have poorer RFS and OS than patients without organ invasion, especially with significant difference of RFS or OS between single- and dual-organ invasion[24]. Tamura et al. suggested a new tumor classification system that combined both layer-based and depth-based systems, indicating the invasion of duodenum or pancreas as a significant independent factor for recurrence[28]. According to their findings, adjacent organ invasion could enhance prognosis prediction in advanced T stages. In the present study, only patients with early stage, T1, were included, and we found that involvement of the pancreas did not affect prognosis, as did duodenum or gallbladder.

To the best of our knowledge, the benefit of adjuvant therapy in DBC is controversial. There are four RCTs comparing adjuvant chemotherapy to observation in patients with resected biliary tract cancer in curative intent. Ebata et al. reported that there was no statistical difference of survival probability in patients undergoing adjuvant gemcitabine chemotherapy

after curative resection of extrahepatic bile duct cancer[33]. In PRODIGE-12 trial, which consisted of intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder cancer, there was no survival benefit of adjuvant gemcitabine and oxaliplatin[34]. On the contrary, BILCAP study showed improved survival of patients with adjuvant capecitabine after resection of cholangiocarcinoma and gallbladder cancer[35]. ASCOT trial also demonstrated a significant improvement in survival in adjuvant S-1 patients with resected cholangiocarcinoma, gallbladder cancer and ampullary cancer[36]. Study population of these trials consisted of heterogenous disease location and stage, so it is unclear if adjuvant chemotherapy can become standard care in DBC. There are retrospective studies with propensity-score matching only including distal cholangiocarcinoma, however, which result is inconsistent with the efficacy of adjuvant chemotherapy on survival[37,38]. In another retrospective study of patients with DBC after R0 resection, Kim et al. showed the result that adjuvant chemotherapy or chemoradiotherapy had improvement in survival[39]. In our study, survival analysis was performed according to the adjuvant therapy. Our result showed adjuvant therapy does not seem to have oncologic benefit with T1 stage with involvement of adjacent organ. When it comes to T1N0 stage, there is no benefit from adjuvant therapy. Consequently, it appears to be no rationale for adjuvant therapy in patients with DBC stage I.

In this study, lymphovascular invasion and lymph node metastasis were identified to have a negative impact on the prognosis of T1 stage DBC. These factors have been considered to be prognostic factors in previous studies. Lymph node metastasis has known for one of the strongest predictors for survival reported in many studies[13,19,20,40-44]. However, several studies have shown different results regarding the predictive value of presence of lymphovascular invasion in DBC[19,20,45]. Kim et al. there was no statistically significant difference in OS between patients with and without lymphovascular invasion in intrapancreatic cholangiocarcinoma after PD[19]. Kwon et al. investigated the prognostic factors for middle and

distal bile duct cancer after bile duct resection or PD[20]. They found that lymphovascuar invasion was associated with the depth of invasion and the presence of lymphovascular invasion affect survival in patients without nodal metastasis. Prognostic factors such as presence of perineural invasion, poor differentiation, high tumor grade were also reported to lower survival outcome of DBC[13,41,43].

Among the risk factors for survival, R0 resection is the only variable that can be controlled through clinical practice. Few studies have shown that R0 resection is not associated with survival[46,47]. One had a mixed tumor biology, with only 38% of patients undergoing PPPD for DBC[46], and another study reported that additional resection margins for R0 resection only in lymph node positive cases did not provide a survival benefit[47]. However, most of the current research emphasized the importance of R0 resection in DBC[20,27,44,48-52]. R0 resection, even after further resection for negative resection margin, was reported to have a significant impact on survival[29]. The results of this study, including T1 patients only, R1 resection was found to have a significant impact on survival with an HR of 2.09 on multivariate analysis. Therefore, R0 resection should be a priority goal for surgeons.

Invasion of ampulla of Vater was associated with a significantly lower HR of 0.49 for 5-year OS and 0.50 for 5-year RFS on multivariate analysis, that was unexpected result. If there is an ampulla invasion, it would be expected that the diagnosis would be earlier because symptoms such as jaundice are more readily apparent. This could be associated with a higher survival rate as they are able to receive appropriate treatment before the disease progresses further.

The limitations of this study are that it is a retrospective study, which is subject to selection bias. To overcome this limitation, we retrospectively collected only patients with both AJCC 7th and 8th edition T staging and excluded patients with only one or the other.

Since this study is based on EMR data only, central pathologic review was not available. Additionally, there was insufficient data on the gross morphology of the tumor such as size or type to include it in the analysis. The number of patients with N2 stage and radiation therapy is insufficient for statistical analysis. In addition, the analysis of adjuvant therapy is insufficient to fully interpret due to lack of consensus on adjuvant treatment and lack of details such as chemotherapy regimen and modality protocol of each center.

Despite these limitations, the fact that this was a multicenter trial that managed to overcome the rarity of DBC and collect a data of a sizable patient population with T1 stage makes the study significant. Previous studies have focused on the biliary tract cancer patient population, showing the heterogeneous nature of perihilar cholangiocarcinoma and DBC, but this study included only DBC. Additionally, it demonstrated that adjuvant therapy at the T1 stage had no survival benefit on the nature course of DBC after curative-intent operation.

Conclusion

In conclusion, the survival impact of organ invasion in patients with DBC T1 stage was not demonstrated by this research. It is in line with the depth-based system of AJCC 8th staging.

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국문요약

원위부 담도암의 T1 병기에서의 췌장 침범에 대한 임상적 의미 및 장기 생존율과 연관된 예후인자 분석을 위한 국내 다기관 연구

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서론: 원위부 담도암의 병기 T stage는 AJCC 7판에서 인접 장기 침범이 기준이었으나 AJCC 8판에서 침범 깊이를 기준으로 개정되었다. 그러나 원위부 담도 주변 장기의 침범이 여전히 임상적으로 의미가 있고, 담도암의 예후에 영향을 미친다는 점에서 담도암 병기설정 시스템의 적정성에 대한 논란이 있었다. 본 연구는 T1 병기에서 담도암의 췌장 침범이 임상적으로 지니는 의미를 평가하고, pT1 병기의 담도암에서 장기 생존과 관련된 예후 인자를 분석하는 것을 목표로 하였다.

방법: 본 연구는 국내 6개 3차 병원이 참여한 후향적 다기관 연구이다. 2009년부터 2019년까지 각 센터에서 췌십이지장 절제술을 받은 원위부 담도암 환자 중 AJCC 8판의 pT1 병기로 진단된 환자를 대상으로 하였다. 제1결과로 5년 무재발 pT1 병기의 생존율(recurrence-free survival)과 전체 생존율(overall survival)을 분석하였다. 제2결과로 원위부 담도암의 pT1 병기의 예후인자에 대한 다변량 분석을 시행하였다.

결과: 총 287명의 환자가 본 연구에 포함되었다. 원위부 담도암의 pT1 병기의 5년 전체 생존율은 63.9% (95% 신뢰구간[confidence interval; CI]: 0.582-0.702), 5년 무재발 생존율은 56.2%(95% CI: 0.502-0.629) 였다. 췌장 침범 여부에 따라 생존 분석을 하였을 때, 5년 전체 생존율(췌장 침범이 없는 그룹 69.9% vs. 췌장 침범이 있는 그룹 54.1, p=0.25) 및 5년 무재발 생존율(췌장 침범이 없는 그룹 56.3% vs. 췌장 침범이 있는 그룹 55.4%, p=0.97)로 확인되어 췌장 침범에 따른 장기적 예후에 유의한 차이는 없었다. 다변량 분석에서 전체 생존율과 관련된 요인은 남성(위험비[hazard ration; HR]: 1.92, CI 1.23-3.01, p=0.004), 연령(HR: 1.03, CI 1.01-1.06, p=0.007), 바터 팽대부 침범(HR: 0.49, CI 0.27-0. 90, p=0.20), 림프혈관 침범(HR: 2.15, CI 1.43-3.23, p<0.001), R1 절제(HR: 2.09, CI 1.07-4.10, p=0.031) 및 N 병기(N1; HR: 2.09 CI 1.28-3.42, p=0.003, N2; HR: 4.94, CI 2.14-11.4, p<0.001) 였다. 전체 생존율의 예후인자 중 남성(HR: 1.87, CI 1.20-2.92, p=0.005), 바터의 앰풀라 침범(HR: 0.50, CI 0.29-0.87, p=0.015), 림프혈관 침범(HR: 2.07, CI 1.39-3.06, p<0.001) 및 N1 병기(HR: 2.23, CI 1.39-3.56, p<0.001) 요인은 다변량 분석을 통해 무재발 생존율과도 유의한 연관성이 있었다.

결론: 원위부 담도암의 pT1 병기에서 췌장 침범이 장기적인 예후에 미치는 영향은 본 연구에서 확인되지 않았다. 이는 AJCC 8판 병기의 기준인 침범 깊이 기반으로 한 T staging 시스템을 지지하는 결과로 보인다.

중심단어: 원위부 담도암, pT1 병기, 췌장 침범, 생존 분석, 예후인자