

Predictors of Unresectable Proximal Cholangiocarcinoma in Potentially Resectable Patients

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Background: Although advanced imaging technique is being used nowadays, the unresectable rate of cholangiocarcinoma has been 38% in patients who have undergone exploration because of sub-radiological metastases.

Objective: To identify the predictors of unresectable proximal cholangiocarcinoma in era of modern imaging.

Materials and Methods: Between January 2012 and April 2017, patients who had potentially curative resection and underwent laparotomy for proximal cholangiocarcinoma were evaluated. The 60 patients were categorized into two groups, resectable and unresectable group.

Results: For an intrahepatic cholangiocarcinoma [ICC] group of 18-unresectable and 27-resectable patients, there were significantly higher levels of alkaline phosphatase [ALP] (328.4 versus 148.8 U/L, $p = 0.002$), gamma-glutamyl transferase [GGT] (364.1 versus 179.9 U/L, $p = 0.015$) and a higher number of patients with N2-enlarged lymph nodes [LN] greater than 1 cm from imaging (27.8% versus 0%, $p = 0.004$) in unresectable group. For a perihilar cholangiocarcinoma [PHC] group of 5-unresectable and 10-resectable patients, there was a higher number of patients with N2-enlarged LN greater than 1 cm from imaging (40.0% versus 0%, $p = 0.032$) in unresectable group. According to univariate analysis, ALP and GGT of resectable group and unresectable group were significantly different by using cut-off level of ALP at 150 U/L (odds ratio 0.240, $p = 0.028$) and GGT level at 240 U/L (odds ratio 0.154, $p = 0.005$). The GGT was the only one independent predictor by using cut-off level at 240 U/L (odds ratio 0.154, $p = 0.13$). The area under the receiver operating characteristic [ROC] curve of GGT was 0.7127.

Conclusion: The GGT was the moderate powerful predictor of unresectable patients for ICC in patients with high a serum level of GGT more than 240 U/L.

Keywords: Intrahepatic cholangiocarcinoma, Perihilar cholangiocarcinoma, Cholangiocarcinoma, Unresectable

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Cholangiocarcinoma is tumor originating from bile duct epithelium and classified by using anatomical position including intrahepatic, perihilar, and distal cholangiocarcinoma⁽¹⁾. The proximal bile duct cancer is comprised of intrahepatic cholangiocarcinoma [ICC], perihilar cholangiocarcinoma [PHC], and gallbladder cancer⁽²⁾. ICC is the second most common primary liver tumor that originates from intrahepatic bile duct and has the worst prognosis of any liver tumor⁽³⁾. Thailand has had the highest incidence rate of cholangiocarcinoma of 100/100,000 associated with liver fluke⁽¹⁾. Although thin-section computed tomography [CT] and magnetic resonance imaging [MRI] technique has been used nowadays, the

resectable rate has been 62% in patients who have undergone exploration because of sub-radiological metastases⁽⁴⁾. Laparoscopic staging has been used to detect occult metastatic disease and avoidance of unnecessary laparotomy⁽⁴⁻⁶⁾. However, routine staging laparoscopy still has controversy and no exact indication^(5,7). The purpose of this study was to identify the predictors of unresectable proximal cholangiocarcinoma in era of modern imaging.

Material and Method

Study population

This was a retrospective study. Sixty-seven consecutive patients who had potentially curative resection without suspected metastatic lesions from radiologic staging that underwent laparotomy for ICC and PHC between January 2012 and April 2017 at Hepato-Pancreato-Biliary Division, Department of Surgery, Ramathibodi Hospital were evaluated.

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Gallbladder cancer was excluded from the study. All patients had histologic confirmation from pre-, intra-, or post-operative.

Definition used

ICC is a tumor originating from beyond the second order of intrahepatic bile duct⁽⁸⁾ and not involving bifurcation. PHC is a tumor originating from beyond the cystic duct junction to the second order of intrahepatic bile duct⁽⁹⁾. ICC was classified by using Liver Cancer Study Group of Japan [LCSGJ] gross macroscopic classification, mass-forming, periductal-infiltrating, and intraductal growth type⁽¹⁰⁾. Tumor staging was classified according to the American Joint Committee on Cancer eighth edition⁽¹¹⁾. Postoperative complication was evaluated within 30 days after the operation by using the Clavien-Dindo classification⁽¹²⁾. The ICC and PHC were considered unresectable in the presence of 1) peritoneal dissemination, 2) intrahepatic metastases, 3) pathological N2-lymph node [LN] metastases (common hepatic, celiac and para-aortic regions), 4) bilateral or contralateral involvement of portal vein, hepatic artery, 5) bilateral involvement of second order of bile duct, and 6) inadequate future liver remnant⁽¹³⁾.

Statistical analysis

Statistical analysis was calculated by SPSS software version 18 (SPSS Inc., Chicago, IL). Variables were compared by using Chi-square (χ^2) tests and independent samples t-tests. Differences were considered significant at a *p*-value of less than 0.05. Univariate and multivariate logistic regression analysis was calculated by stepwise technique.

Results

From 67 patients, seven patients were excluded due to pathological diagnosis of no malignancy (Figure 1). The remaining 60 patients included 45 patients (74.6%) with ICC and 15 patients (25.4%) with PHC. For ICC patients, 27 patients (59.1%) underwent curative resection and 18 patients (40.9%) could not receive resection after laparotomy. For PHC patients, 10 patients (66.7%) underwent curative resection and five patients (33.3%) could not receive resection after laparotomy.

Patient characteristics

Patients were grouped into two groups, an unresectable group and a resectable group. For ICC and PHC, there were no significant differences between

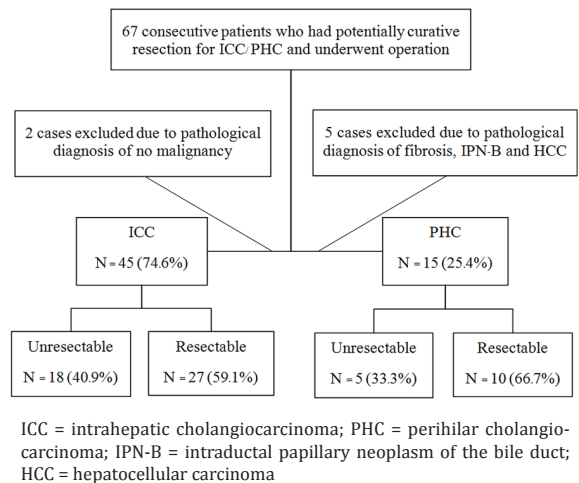


Figure 1. Patient disposition.

the two groups in terms of gender, age, presence of symptoms, body mass index [BMI], duration from first visit to surgery, duration from presence of symptom to surgery, duration from last imaging to surgery, and the American Society of Anesthesiologists score (Table 1). For ICC, there were significantly shorter length of stay (6.9 versus 15.7 days, *p* = 0.009) and operative time (144.7 versus 431.1 minutes, *p* = 0.002) in unresectable group. Additionally, there were significantly lower estimated blood loss (211.9 versus 1,187.0 mL, *p* = 0.001), blood transfusion (0 versus 1.2 unit; *p* = 0.001), and postoperative complication (11.1% versus 51.9%, *p* = 0.005) in unresectable group. For PHC, there were significantly shorter operative time (239.0 versus 605.5 minutes, *p* = 0.002), lower estimated blood loss (620 versus 1,960 mL, *p* = 0.006), and lower blood transfusion (0.4 versus 2.7 unit, *p* = 0.008) in unresectable group.

Preoperative blood sampling data

For ICC and PHC, in terms of preoperative blood sampling, no significant differences of total bilirubin, albumin, carcinoembryonic antigen [CEA], and carbohydrate antigen 19-9 [CA19-9] between unresectable group and resectable group were discovered (Table 2). However, for ICC, there were significantly higher levels of alkaline phosphatase [ALP] (328.4 versus 148.8, *p* = 0.002) and gamma-glutamyl transferase [GGT] (364.1 versus 179.9, *p* = 0.015) in unresectable group.

Preoperative imaging data

For both ICC and PHC, there were no significant

differences of imaging technique, slice thickness, dynamic phase, vascular invasion, adjacent organ invasion, T staging, tumor size and gross morphology. However, for ICC and PHC, unresectable group was

Table 1. Patient characteristics

	Intrahepatic cholangiocarcinoma			Perihilar cholangiocarcinoma		
	Unresectable (n = 18)	Resectable (n = 27)	p-value	Unresectable (n = 5)	Resectable (n = 10)	p-value
Gender, n (%)			0.616			0.121
Male	12 (66.7)	16 (59.3)		2 (40.0)	8 (80.0)	
Female	6 (33.3)	11 (40.7)		3 (60.0)	2 (20.0)	
Age (years), mean	60.2	63.0	0.377	61.2	55.7	0.261
Symptoms, n (%)			0.083			0.829
Asymptomatic	2 (11.1)	10 (37.0)		1 (20.0)	1 (20.0)	
Weight loss	4 (22.2)	1 (3.7)		0 (0.0)	0 (0.0)	
Abd. discomfort	12 (66.7)	12 (44.4)		1 (20.0)	3 (30.0)	
Abd. mass	0 (0.0)	2 (7.4)		0 (0.0)	0 (0.0)	
Jaundice	0 (0.0)	1 (3.7)		3 (60.0)	6 (60.0)	
Other	0 (0.0)	1 (3.7)		0 (0.0)	0 (0.0)	
1 st visit-BMI (kg/m ²), mean	24.82	24.72	0.929	25.06	22.56	0.240
BS-BMI (kg/m ²), mean	23.85	24.57	0.552	24.30	20.55	0.138
D-BMI (kg/m ²), mean	-0.98	-0.15	0.059	-0.76	-2.01	0.387
Duration from 1 st visit* (day)	60.6	49.0	0.344	102.0	119.1	0.780
Duration of symptom** (day)	120.8	98.9	0.438	140.4	156.6	0.791
Duration from imaging*** (day)	50.0	46.7	0.640	37.2	49.4	0.466
Length of stay (days), mean	6.9	15.7	0.009	10.6	18.8	0.070
Operative time (minutes), mean	144.7	431.1	0.002	239.0	605.5	0.002
Estimated blood loss (mL), mean	211.9	1,187.0	0.001	620.0	1,960.0	0.006
Blood transfusion (unit), mean	0.0	1.2	0.001	0.4	2.7	0.008
Major liver resection, n (%)	0 (0.0)	15 (55.6)	0.003	1 (20.0)	9 (90.0)	0.007
ASA, n (%)			0.472			0.409
Class I	1 (5.6)	1 (3.7)		0 (0.0)	0 (0.0)	
Class II	9 (50.0)	9 (33.3)		2 (40.0)	2 (20.0)	
Class III	8 (44.4)	17 (63.0)		3 (60.0)	8 (80.0)	
Complication, n (%)	2 (11.1)	14 (51.9)	0.005	2 (40.0)	6 (60.0)	0.464
Grade I	0 (0.0)	7 (50.0)		0 (0.0)	1 (16.7)	
Grade II	1 (50.0)	3 (21.4)		1 (50.0)	1 (16.7)	
Grade IIIa	0 (0.0)	1 (7.1)		1 (50.0)	3 (50.0)	
Grade IIIb	0 (0.0)	3 (21.4)		0 (0.0)	0 (0.0)	
Grade IV	1 (50.0)	0 (0.0)		0 (0.0)	1 (16.7)	
Grade V	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Abd. = abdominal; BS-BMI = before surgery body mass index; D-BMI = delta-body mass index (before surgery BMI minus 1st visiting BMI); ASA = American Society of Anesthesiologists

* Duration from 1st visit to surgery, ** Duration from presence of symptom to surgery, *** Duration from last undergone imaging to surgery

Table 2. Preoperative blood sampling data

	Intrahepatic cholangiocarcinoma			Perihilar cholangiocarcinoma		
	Unresectable (n = 18)	Resectable (n = 27)	p-value	Unresectable (n = 5)	Resectable (n = 10)	p-value
Tbil (mg/dL), mean	0.6	0.2	0.192	1.0	1.8	0.176
Albumin (g/L), mean	34.6	36.8	0.179	37.1	34.5	0.130
ALP (U/L), mean	328.4	148.8	0.002	332.0	388.7	0.674
GGT (U/L), mean	364.1	179.9	0.015	455.8	595.9	0.384
CEA (ng/mL), mean	25.0	50.7	0.413	2.8	60.1	0.546
CA19-9 (U/mL), mean	1,952.0	3,311.2	0.566	685.8	1,575.5	0.580

Tbil = total bilirubin; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; CEA = carcinoembryonic antigen; CA19-9 = carbohydrate antigen 19-9

Table 3. Preoperative imaging data

	Intrahepatic cholangiocarcinoma			Perihilar cholangiocarcinoma		
	Unresectable (n = 18)	Resectable (n = 27)	p-value	Unresectable (n = 5)	Resectable (n = 10)	p-value
Imaging tech., n (%)			0.054			-
CT	16 (88.9)	17 (63.0)		5 (100)	10 (100)	
MRI	2 (11.1)	10 (37.0)		0 (0.0)	0 (0.0)	
Slice thickness, n (%)			0.304			0.264
<3 mm	5 (27.8)	9 (33.3)		4 (80.0)	5 (50.0)	
>3 mm	13 (72.2)	18 (66.7)		1 (20.0)	5 (50.0)	
Dynamic phase, n (%)			0.693			0.591
Triple phases	13 (72.2)	15 (55.6)		4 (80.0)	9 (90.0)	
Tetra phases	5 (27.8)	12 (44.4)		1 (20.0)	1 (10.0)	
Vas. invasion, n (%)	8 (44.4)	7 (25.9)	0.197	0 (0.0)	0 (0.0)	-
Adj. organ abutment or invasion, n (%)	9 (50.0)	11 (40.7)	0.540	1 (33.3)	0 (0.0)	0.134
T staging, n (%)			0.502			0.373
T1a	2 (11.1)	8 (30.8)		0 (0.0)	0 (0.0)	
T1b	3 (16.7)	4 (15.4)		0 (0.0)	0 (0.0)	
T2	4 (22.2)	3 (11.5)		0 (0.0)	0 (0.0)	
T2a	0 (0.0)	0 (0.0)		1 (20.0)	4 (40.0)	
T2b	0 (0.0)	0 (0.0)		2 (40.0)	5 (50.0)	
T3	6 (33.3)	9 (34.6)		2 (40.0)	1 (10.0)	
T4	3 (16.7)	2 (7.7)		0 (0.0)	0 (0.0)	
Tumor size (mm), mean	63.3	71.4	0.416	-	-	-
Gross morph., n (%)			0.231			0.392
Mass forming	18 (100)	23 (85.2)		0 (0.0)	1 (10.0)	
Intraductal	0 (0.0)	3 (11.1)		0 (0.0)	2 (20.0)	
Periductal	0 (0.0)	1 (3.7)		5 (100)	7 (70.0)	
N2-LN >1 cm, n (%)	5 (27.8)	0 (0.0)	0.004	2 (40.0)	0 (0.0)	0.032

tech. = technique; Vas. = vascular; Adj. = adjacent; morph. = morphology; LN = lymph node

Table 4. Univariate analysis of predictor of unresectable for ICC

Predictor	Unresectable	Resectable	Odds ratio (95% CI)	p-value
D-BMI (kg/m ²), mean	-0.98	-0.15	1.710 (0.980 to 2.990)	0.059
ALP (U/L), n (%)				0.03
>150	12 (66.7)	9 (33.3)	0.250 (0.070 to 0.890)	
<150	6 (33.3)	18 (66.7)	1	
GGT (U/L), n (%)				0.01
>240	11 (61.1)	5 (18.5)	0.152 (0.040 to 0.590)	
<240	7 (38.9)	22 (81.5)	1	
N2-LN >1 cm, n (%)	5 (27.8)	0 (0.0)	-	0.04

CI = confidence interval; D-BMI = delta-body mass index (before surgery BMI minus 1st visiting BMI); ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase

Table 5. Multivariate analysis of predictor of unresectable for ICC

Predictor	Odds ratio (95% CI)	p-value
GGT (>240 U/L versus <240 U/L)	0.150 (0.040 to 0.590)	0.001

GGT = gamma-glutamyl transferase

a higher number of patients with N2-enlarged LN greater than 1 cm from imaging, 27.8% versus 0%, $p = 0.004$ in ICC and 40% versus 0%, $p = 0.032$ in PHC group (Table 3).

Univariate and multivariate analysis

Univariate analysis was calculated by using delta-body mass index [D-BMI], ALP and GGT. Only two variables, ALP and GGT, were significantly different by using cut-off level of ALP at 150 U/L (50 percentile) and cut-off level of GGT at 240 U/L (75 percentile). The odds ratio for ALP and GGT were 0.240, 0.154 and p -value were 0.028, 0.005, respectively. GGT was only significant predictor after multivariate analysis was done (odds ratio 0.154, $p = 0.013$) (Table 4, 5).

The area under the receiver operating characteristic [ROC] curve of GGT was 0.7127 (Figure 2).

Cause of unresectable

For 18 unresectable patients in ICC group, five patients (27.8%) were found having peritoneal metastases, five patients (27.8%) were found having liver metastases, and one (5.6%) was found having locally advanced tumor after laparotomy. The remaining 7 patients (38.9%) had N2-LN metastases with five cases for para-aortic LN and two cases for celiac LN metastases (Figure 3a).

For five unresectable patients in PHC group, three patients (60%) were unresectable due to locally advanced tumor and two (40%) had para-aortic LN metastases (Figure 3b).

Discussion

In contrast to distal cholangiocarcinoma, ICC usually presents symptoms after advanced stage as there are no tumor markers for early diagnosis^(1,14). The yield of staging depends on the technique and quality of preoperative imaging such as thin slice or thick slice imaging, CT, or MRI⁽⁶⁾. The good quality of preoperative imaging can increase yield of identified small liver metastases or peritoneal metastases and can reduce rate of unresectable laparotomy due to distant metastases⁽¹⁵⁾.

From this study, ICC, the resectable rate in potentially resectable patients was 59.1% comparable to other studies with the rate of 52% to 76%^(15,16). Nowadays, there have been no definite predictors detecting unresectable cholangiocarcinoma. Data analysis of this study revealed that unresectable ICC-patients tended to have a lower body mass index [BMI] and higher weight loss (D-BMI) when compared with resectable ICC-patients but the difference was not statistically significant. Surprisingly, the serum level of ALP and GGT were significantly higher in unresectable group. The ALP and GGT basically have been used as biomarkers for liver diseases and usually rise in hepatic or biliary tract diseases⁽¹⁷⁾. For hepatocellular carcinoma [HCC], the elevation of ALP and GGT in the presence of normal bilirubin is associated with poor overall survival after treatment⁽¹⁸⁾. A previous study indicated that the high level of serum GGT was useful as a biomarker for unfavorable prognosis of ICC after surgery and as an indicator of aggressive tumor behaviors including vascular invasion, LN involvement, and incomplete tumor encapsulation⁽¹⁹⁾. Moreover, from experimental study, cancer cells showed higher

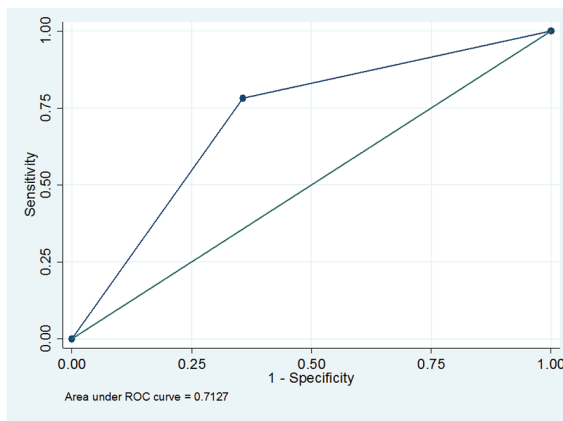


Figure 2. ROC curve of gamma-glutamyl transferase (GGT).

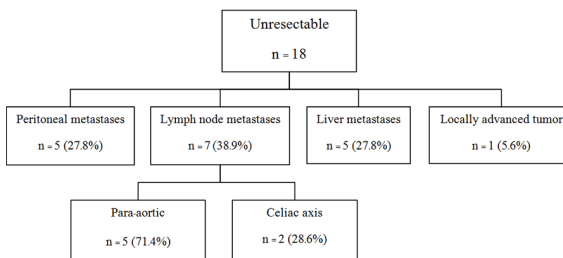


Figure 3a. Cause of unresectable for ICC.

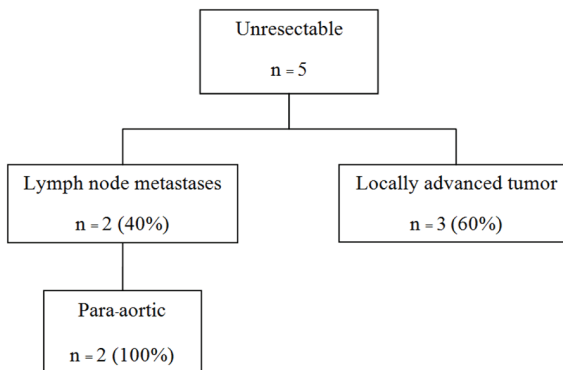


Figure 3b. Cause of unresectable for PHC.

ALP level in the nucleolus during tumor cell proliferation. Therefore, the high level of ALP product should be associated with the high level of cancer cell proliferation⁽²⁰⁾. In terms of GGT, GGT plays as an important enzyme for cell proliferative and apoptotic balance, which have potential implications in tumor progression and drug resistance⁽²¹⁾. To the best of our knowledge, the relationship between GGT and tumor aggressiveness is still unexplainable and needs further experimental studies. According to present study,

univariate analysis was calculated by using the cut-off values of ALP level at 150 U/L and GGT level at 240 U/L. At these cut-off levels, significant differences were found between unresectable group and resectable group. Multivariate analysis showed that GGT was an only independent predictor for unresectable ICC and ROC curve analysis revealed a moderate powerful predictor of GGT with the area under the curve of 0.71. For PHC, no correlation between resectable and unresectable groups was found due to the low sample size.

The limitation of this study was the small sample size especially in the PHC group. Although Thailand has had the highest incidence of cholangiocarcinoma, the high incidence is only found in north-east of Thailand. The incidence of cholangiocarcinoma in central part of Thailand is six times less than that in north-eastern part⁽³⁾. Retrospective data collection for more than five years might have more sample size but the obtained data might be unreliable due to the poor preoperative radiologic imaging quality. This was the reason this study conducted retrospective data collection for five years only.

Conclusion

The GGT was a moderate powerful predictor of unresectable patients for ICC in patients with a high serum level of GGT of more than 240 U/L.

What is already known on this topic?

The unresectable rate of ICC after laparotomy is high, due to disseminated disease. Nowadays, the predictors of unresectable ICC has not been documented. According to previous studies, the GGT was useful as a biomarker for unfavorable prognosis of ICC after surgery and as an indicator of aggressive tumor behaviors.

What this study adds?

From this study, GGT can be used as a predictor of unresectable patients for ICC. Furthermore, GGT is a moderate powerful predictor in patients with a high serum level of GGT of more than 240 U/L.

Potential conflicts of interest

None.

References

1. Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut* 2002;51(Suppl 6):VII-9.
2. Hariharan D, Constantinides VA, Froeling FE, Tekkis PP, Kocher HM. The role of laparoscopy and laparoscopic ultrasound in the preoperative staging of pancreatico-biliary cancers—A meta-analysis. *Eur J Surg Oncol* 2010;36:941-8.
3. Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang Y, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma—focus on East and South-Eastern Asia. *Asian Pac J Cancer Prev* 2010;11:1159-66.
4. Weber SM, Jarnagin WR, Klimstra D, De Matteo RP, Fong Y, Blumgart LH. Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. *J Am Coll Surg* 2001;193:384-91.
5. Goere D, Wagholikar GD, Pessaux P, Carrere N, Sibert A, Vilgrain V, et al. Utility of staging laparoscopy in subsets of biliary cancers: laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma. *Surg Endosc* 2006;20:721-5.
6. Weber SM, De Matteo RP, Fong Y, Blumgart LH, Jarnagin WR. Staging laparoscopy in patients with extrahepatic biliary carcinoma. Analysis of 100 patients. *Ann Surg* 2002;235:392-9.
7. Ruys AT, Busch OR, Gouma DJ, van Gulik TM. Staging laparoscopy for hilar cholangiocarcinoma: is it still worthwhile? *Ann Surg Oncol* 2011;18:2647-53.
8. Yang J, Yan LN. Current status of intrahepatic cholangiocarcinoma. *World J Gastroenterol* 2008;14:6289-97.
9. Miyazaki M, Ohtsuka M, Miyakawa S, Nagino M, Yamamoto M, Kokudo N, et al. Classification of biliary tract cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery: 3rd English edition. *J Hepatobiliary Pancreat Sci* 2015;22:181-96.
10. Yamasaki S. Intrahepatic cholangiocarcinoma: macroscopic type and stage classification. *J Hepatobiliary Pancreat Surg* 2003;10:288-91.
11. Spolverato G, Bagante F, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L, et al. Comparative performances of the 7th and the 8th editions of the American Joint Committee on Cancer staging systems for intrahepatic cholangiocarcinoma. *J Surg Oncol* 2017.
12. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo

- classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187-96.
13. Schulick RD. Criteria of unresectability and the decision-making process. *HPB (Oxford)* 2008;10: 122-5.
 14. Thunyaharn N, Promthet S, Wiangnon S, Suwanrungruang K, Kamsa-ard S. Survival of cholangiocarcinoma patients in northeastern Thailand after supportive treatment. *Asian Pac J Cancer Prev* 2013;14:7029-32.
 15. Lang H, Sotiropoulos GC, Sgourakis G, Schmitz KJ, Paul A, Hilgard P, et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. *J Am Coll Surg* 2009; 208:218-28.
 16. Guglielmi A, Ruzzenente A, Campagnaro T, Pachera S, Valdegamberi A, Nicoli P, et al. Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. *World J Surg* 2009;33: 1247-54.
 17. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci* 2001;38:263-355.
 18. Xu XS, Wan Y, Song SD, Chen W, Miao RC, Zhou YY, et al. Model based on gamma-glutamyltransferase and alkaline phosphatase for hepatocellular carcinoma prognosis. *World J Gastroenterol* 2014;20:10944-52.
 19. Yin X, Zheng SS, Zhang BH, Zhou Y, Chen XH, Ren ZG, et al. Elevation of serum gamma-glutamyltransferase as a predictor of aggressive tumor behaviors and unfavorable prognosis in patients with intrahepatic cholangiocarcinoma: analysis of a large monocenter study. *Eur J Gastroenterol Hepatol* 2013;25:1408-14.
 20. Yamamoto K, Awogi T, Okuyama K, Takahashi N. Nuclear localization of alkaline phosphatase in cultured human cancer cells. *Med Electron Microsc* 2003;36:47-51.
 21. Pompella A, Corti A, Paolicchi A, Giommarelli C, Zunino F. Gamma-glutamyltransferase, redox regulation and cancer drug resistance. *Curr Opin Pharmacol* 2007;7:360-6.

ปัจจัยที่บ่งบอกถึงการผ่าตัดไม่สำเร็จในผู้ป่วยที่คาดว่าสามารถผ่าตัดได้ต่อการรักษามะเร็งท่อน้ำดีส่วนต้น

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ภูมิหลัง: แม้ว่าการตรวจวินิจฉัยทางรังสีวิทยามีความก้าวหน้าขึ้นมาก แต่พบว่ามีผู้ป่วยโรคมะเร็งท่อน้ำดี จำนวนหนึ่ง (38%) ไม่สามารถผ่าตัด เนื่องจากพบว่ามีกระจายของมะเร็งไปยังต่อมน้ำเหลือง เชื้อบุช่องท้องหรือในตับ แม้ว่าจะไม่พบการกระจายของโรคจากภาพรังสีวิทยาก็ตาม

วัตถุประสงค์: เพื่อหาปัจจัยที่บ่งบอกถึงการผ่าตัดไม่สำเร็จของโรคมะเร็งท่อน้ำดีส่วนต้นในยุคสมัยปัจจุบันที่มีภาพทางรังสีวิทยาคุณภาพดี

วัสดุและวิธีการ: ผู้ป่วยมะเร็งท่อน้ำดีส่วนต้นที่ได้รับการผ่าตัดระหว่าง เดือนมกราคม พ.ศ. 2555 ถึง เมษายน พ.ศ. 2560 ที่คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี จำนวนทั้งสิ้น 60 ราย แบ่งเป็น 2 กลุ่ม คือ กลุ่มผู้ป่วยโรคมะเร็งท่อน้ำดีที่สามารถผ่าตัดได้ และกลุ่มผู้ป่วยมะเร็งท่อน้ำดีที่ไม่สามารถผ่าตัดได้

ผลการศึกษา: ในผู้ป่วยมะเร็งท่อน้ำดีชนิดในตับ (intrahepatic cholangiocarcinoma) ทั้งหมด 45 ราย แบ่งเป็นกลุ่มที่สามารถผ่าตัดได้ 27 ราย และกลุ่มที่ไม่สามารถผ่าตัดได้ 18 ราย พบว่าการตรวจค่าการทำงานของตับ alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT] สูงกว่าในกลุ่มที่ไม่สามารถผ่าตัดได้ (328.4 ต่อ 148.8 U/L, $p = 0.002$ และ 364.1 ต่อ 179.9 U/L, $p = 0.015$ ตามลำดับ) และพบว่าผู้ป่วยที่ไม่สามารถผ่าตัดได้มักจะมีต่อมน้ำเหลืองกลุ่ม N2 ขนาดใหญ่กว่า 1 เซนติเมตร จากภาพถ่ายรังสีมากกว่ากลุ่มที่ผ่าตัดได้อย่างมีนัยสำคัญทางสถิติ (27.8% ต่อ 0%, $p = 0.004$) ส่วนกลุ่มผู้ป่วยมะเร็งท่อน้ำดีชนิดขั้วตับ (perihilar cholangiocarcinoma) มีจำนวนทั้งหมด 15 ราย แบ่งเป็นกลุ่มที่สามารถผ่าตัดได้ 10 ราย และกลุ่มที่ไม่สามารถผ่าตัดได้ 5 ราย พบว่าผู้ป่วยที่ไม่สามารถผ่าตัดได้มักจะมีต่อมน้ำเหลืองกลุ่ม N2 ที่มีขนาดใหญ่กว่า 1 เซนติเมตร จากภาพถ่ายรังสีมากกว่ากลุ่มที่ผ่าตัดได้อย่างมีนัยสำคัญทางสถิติ (40% ต่อ 0%, $p = 0.032$) จากการวิเคราะห์ข้อมูลแบบ univariate พบว่าค่า ALP และ GGT สามารถแยกกลุ่มที่สามารถผ่าตัดได้ออกจากกลุ่มที่ไม่สามารถผ่าตัดได้เมื่อใช้ค่า ALP ที่ 150 U/L และ GGT ที่ 240 U/L ตามลำดับ แต่เมื่อวิเคราะห์ด้วย multivariate พบว่ามีเฉพาะค่า GGT ตัวเดียวที่สามารถใช้แยกกลุ่มที่สามารถผ่าตัดได้ออกจากกลุ่มที่ไม่สามารถผ่าตัดได้ และจากการคำนวณพื้นที่ใต้กราฟ (ROC curve) พบว่า GGT มีพื้นที่ใต้กราฟอยู่ที่ 0.7127

สรุป: GGT สามารถใช้พยากรณ์การผ่าตัดไม่สำเร็จได้โดยมีความน่าเชื่อถือที่ระดับปานกลางสำหรับโรคมะเร็งท่อน้ำดีชนิดในตับเมื่อใช้ค่า GGT สูงกว่า 240 U/L แต่ในโรคมะเร็งท่อน้ำดีชนิดขั้วตับยังคงต้องรอข้อมูลเพิ่มเติม
