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Original Article

# *Survival and Treatment Outcomes of Resectable Cholangiocarcinoma: Initial Experience in Khon Kaen Hospital*

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***Abstract***

***Background:*** The most effective current treatment for cholangiocarcinoma is surgical resection. Khon Kaen Hospital receives a significant number of cholangiocarcinoma patients, and it is essential to analyze the treatment outcomes and survival to improve future treatment processes.

***Methods:*** A retrospective study that analyzes the treatment outcomes and survival of cholangiocarcinoma patients who underwent surgery at Khon Kaen Hospital between October 2014 to September 2019. The study covers patient demographics, disease characteristics, surgical information, treatment outcomes, complications, and survival analysis.

***Results:*** There were a total of 84 predominantly male patients with an average age of 63 years. Most patients had intrahepatic type and presented with abdominal pain and jaundice. The most common complication was wound infection, 14%, and the overall perioperative mortality rate was 8%. The perihilar type had the highest mortality rate. The median survival time was 16.8 months, with the intrahepatic type having the most prolonged survival (23.2 months), followed by distal type (16.5 months) and perihilar type (9.2 months). These differences were statistically significant ($P$-value < 0.01). Positive margins and lymph node involvement were significant factors associated with shorter survival times.

***Conclusion:*** Surgical treatment of cholangiocarcinoma at Khon Kaen Hospital is generally safe, with complication and mortality rates comparable to other research studies. Key factors for long-term survival include achieving a negative microscopic margin (R0 resection) and the absence of lymph node involvement.

***Keywords:*** Cholangiocarcinoma surgery

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## Introduction

Currently, the incidence of bile duct cancer is increasing worldwide, accounting for approximately 3% of gastrointestinal cancers. Cholangiocarcinoma is highly prevalent in Thailand, especially in the northeastern region, with incidence rates of approximately 89.5 per 100,000 males and 35.5 per 100,000 females.[1] At present, Cholangiocarcinoma is categorized based on its location, namely, intrahepatic, perihilar, and distal cholangiocarcinoma. Most patients (60-70%) fall into the perihilar type category.[2,3] The most effective treatment for cholangiocarcinoma is surgical resection. This procedure has resulted in 5-year overall survival rates ranging from 10-20% for intrahepatic type, 10-40% for perihilar type, and 23-50% for distal type.[4-10] Median survival time ranging from 20-30 months for intrahepatic type, 12-24 months for perihilar type, and 24-36 months for distal type.[4-10] Surgical resection is a complex procedure associated with high morbidity, reaching up to 17-63%, and perioperative mortality 5-10%.[4-10] Khon Kaen Hospital, a major tertiary care center in the northeastern region of Thailand, plays a crucial role in treating. This situation prompted the researchers to analyze detailed treatment outcomes for cholangiocarcinoma patients at Khon Kaen Hospital. The study covers disease characteristics, patient demographics, surgical data, survival duration, complications, and in-hospital mortality rates. This analysis aims to serve as a foundation for future improvements in treatment and enhance patient outcomes.

## Materials and Methods

This study is a descriptive retrospective study and survival analysis. The data was collected from 84 patients diagnosed with cholangiocarcinoma who underwent surgical treatment at the Department of Surgery, Khon Kaen Hospital, between October 2014 to September 2019. This data included patient characteristics, disease characteristics, surgical information, treatment outcomes, complications, and survival times. Analyze and summarize this data to produce research findings for dissemination to interested parties (Figure 1).

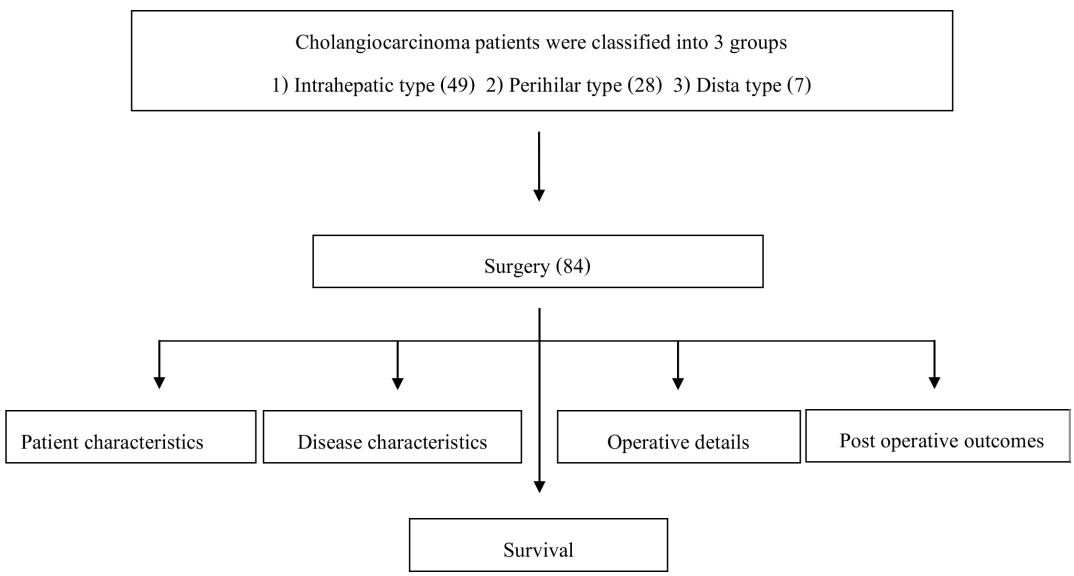


Figure 1

## Results

Among patients with cholangiocarcinoma who received surgical treatment at the Department of Surgery, Khon Kaen Hospital, during the 5-year data collection period, a total of 84 cases were identified. The majority of these cases were found to be of the intrahepatic type 49 (58%), followed by the perihilar type 28 (33%), and finally the distal type 7 (8%). Most patients were male, with a male-to-female ratio of 7:3. The average age was 63 years (25-79). The average body mass index (BMI) was 22.2 (18.5 to 25.8).

The most common accounting presenting symptom among patients for 28 (33%) is abdominal pain. This is the predominant symptom in the overall patient population

and the primary symptom in the intrahepatic type. The second most common symptom, observed in 22 (26%), is jaundice, characterized by yellowing of the skin and eyes. This is the major symptom in the perihilar type and the distal type. There is a statistically significant difference between these two groups (*P*-value < 0.01).

The majority of patients had an American Society of Anesthesiologists (ASA) score of I, II 52 (61.9%) or III, IV 32 (38.1%). Regarding laboratory findings, levels of total bilirubin, liver enzymes (AST, ALT), alkaline phosphatase (ALP), and serum albumin (Alb) were found to be higher in patients with perihilar type and distal type compared to those with intrahepatic type. There was a statistically significant difference in these laboratory parameters among the different tumor locations ($p < 0.001$). By patient characteristics, presenting symptoms, and laboratory findings according to the location of bile duct cancer, the data is presented in Table 1.

**Table 1** Patient characteristics and laboratory results by location.

| Clinical characteristics | Overall (n = 84) | Intrahepatic (n = 49) | Perihilar (n = 28) | Distal (n = 7) | *P*-value |
|---|---|---|---|---|---|
| **Male sex, n (%)** | 59 (70.2) | 31 (63.3) | 21 (75.0) | 7 (100.0) | 0.12 |
| **Age, Median (min:max)** | 63 (25:79) | 64 (35:79) | 60 (26:76) | 58 (25:71) | 0.02* |
| **BMI, Mean ± SD** | 22.19 ± 3.64 | 21.95 ± 3.58 | 22.50 ± 3.54 | 22.64 ± 4.86 | 0.78 |
| **Smoking, n (%)** | 67 (79.8) | 40 (81.6) | 22 (78.6) | 5 (71.4) | 0.70 |
| **No underlying disease, n (%)** | 56 (66.7) | 29 (59.2) | 22 (78.6) | 5 (71.4) | 0.80 |
| **Clinical presentation, n (%)** | | | | | < 0.001* |
| Abdominal pain | 51 (60.7) | 40 (81.6) | 11 (39.3) | 0 (0.0) | |
| Jaundice | 22 (26.2) | 0 (0.0) | 16 (57.1) | 6 (85.7) | |
| Weight loss | 4 (4.8) | 3 (6.1) | 1 (3.6) | 0 (0.0) | |
| Fever | 3 (3.6) | 2 (4.1) | 0 (0.0) | 1 (14.3) | |
| **Previous abdominal surgery, n (%)** | 5 (6.0) | 3 (6.1) | 2 (7.1) | 0 (0.0) | 0.77 |
| **ASA Class, n (%)** | | | | | 0.76 |
| I | 9 (10.7) | 6 (12.2) | 3 (10.7) | 0 (0.0) | |
| II | 43 (51.2) | 26 (53.1) | 14 (50.0) | 2 (42.0) | |
| III | 31 (36.9) | 17 (34.7) | 10 (35.7) | 3 (57.1) | |
| IV | 1 (1.2) | 0 (0.0) | 1 (3.6) | 0 (0.0) | |
| **Laboratory information** | | | | | |
| Bilirubin (Mean ± SD) | 6.62 ± 10.97 | 0.88 ± 1.61 | 13.13 ± 14.03 | 10.70 ± 7.92 | < 0.001* |
| Alkaline phosphatase (Mean ± SD) | 207 ± 173.30 | 141.73 ± 92.38 | 255.58 ± 155.65 | 471.42 ± 332.80 | < 0.001* |
| AST (Mean ± SD) | 63.39 ± 63.82 | 41.59 ± 44.38 | 92.21 ± 80.97 | 100.71 ± 41.27 | 0.001* |
| ALT (Mean ± SD) | 60.35 ± 72.27 | 37.79 ± 34.4 | 94.75 ± 107.27 | 80.71 ± 28.83 | < 0.001* |
| Albumin (Mean ± SD) | 4.10 ± 3.25 | 3.86 ± 0.49 | 4.50 ± 5.61 | 3.57 ± 8.11 | < 0.001* |

**P*-value less than 0.05 was statistically significant

From the study results presented in Table 2, it was found that nearly all patients who underwent surgical treatment had adenocarcinoma 81 (98.8%). Among these cases, the majority were classified as well-differentiated, representing 77 (91.7%). Larger tumor sizes > 2 centimeters were predominantly observed in the intrahepatic type 46 (93.9%), which was statistically significantly different from the perihilar and distal types ($p < 0.01$). Additionally, angiolymphatic invasion was observed in 25 (29.8%), and lymph node involvement was noted in 28 (33.3%).

In terms of surgical details, an average of 3.69 ± 3.12 lymph nodes were dissected during surgery. A negative microscopic margin (R0 resection) was achieved in 53 (63.1%). Notably, the likelihood of complete tumor resection was higher in the distal type than in the intrahepatic and perihilar types, with statistically significant differences ($p < 0.01$). In most cases, liver resection was performed in addition to bile duct resection during surgery, particularly in the perihilar type.

**Table 2** Disease characteristics by location.

| Disease characteristics | Overall (n = 84) | Intrahepatic (n = 49) | Perihilar (n = 28) | Distal (n = 7) | *P*-value |
|---|---|---|---|---|---|
| **Tumor histology, n (%)** | | | | | |
| Adenocarcinoma | 83 (98.8) | 49 (100.0) | 27 (96.4) | 7 (100.0) | 0.41 |
| **Degree of differentiation, n (%)** | | | | | |
| Well | 77 (91.7) | 5 (91.8) | 26 (92.9) | 6 (85.7) | 0.72 |
| Moderate | 6 (7.1) | 3 (6.1) | 2 (7.1) | 1 (14.3) | |
| Poor | 1 (1.2) | 1 (2) | 0 (0.0) | 0 (0.0) | |
| **Tumor diameter (> 2 cm), n (%)** | 60 (71.4) | 46 (93.9) | 12 (42.9) | 2 (28.6) | < 0.001* |
| **Angiolymphatic invasion, n (%)** | 25 (29.8) | 12 (24.5) | 12 (42.9) | 1 (14.3) | 0.05 |
| **Negative microscopic margins, n (%)** | 53 (63.1) | 37 (75.5) | 10 (35.7) | 6 (85.7) | 0.001* |
| **Lymph node involvement, n (%)** | 28 (33.3) | 17 (34.7) | 9 (32.1) | 2 (28.5) | 0.93 |
| **Number of retrieved lymph nodes (Mean ± SD)** | 3.69 ± 3.12 | 4.6 ± 3.18 | 2.21 ± 2.51 | 3.14 ± 2.91 | 0.004* |

**P*-value less than 0.05 was statistically significant

Table 3 presents the surgical procedures and perioperative complications observed in all 84 patients. In the group of intrahepatic type, surgical treatment primarily involved anatomical resection of the liver and regional lymphadenectomy. For patients with perihilar type, the surgical approach included extrahepatic bile duct resection, which may also involve anatomical liver resection with or without caudate inclusion, along with regional lymphadenectomy. In the case of the distal type, the surgical procedure typically consisted of pancreaticoduodenectomy, extrahepatic bile duct resection, and regional lymphadenectomy.

The most common complications were wound infection 12 (14.3%), respiratory infection 9 (10.7%), postoperative liver failure 8 (9.5%), biliary leak 5 (5.9%), and pancreatic leak 1 (1.2%). When analyzed by groups, biliary leak was more frequently observed in the perihilar cholangiocarcinoma group. The average duration of surgery was 5 hours and 15 minutes, with an average blood loss of 1,071 milliliters. The overall perioperative mortality rate was 7 (8.3%), with a breakdown of 2 (4.1%) for intrahepatic type, 4 (14.3%) for perihilar type, and 1 (14.3%) for distal type. The main cause of mortality was respiratory infection, followed by postoperative liver failure.

**Table 3** Postoperative complications, operative details, perioperative mortality, and median survival by location

| Postoperative details | Overall (n = 84) | Intrahepatic (n = 49) | Perihilar (n = 28) | Distal (n = 7) | *P*-value |
|---|---|---|---|---|---|
| **Wound infection, n (%)** | 12 (14.3) | 8 (16.3) | 4 (14.3) | 0 (0.0) | |
| **Biliary leak, n (%)** | 5 (5.9) | 2 (4.1) | 3 (10.7) | 0 (0.0) | |
| **Pancreatic leak, n (%)** | 1 (1.2) | 0 (0.0) | 0 (0) | 1 (3.6) | |
| **Sepsis, n (%)** | 3 (3.6) | 3 (6.1) | 0 (0.0) | 0 (0.0) | |
| **Respiratory, n (%)** | 9 (10.7) | 6 (12.2) | 3 (10.7) | 0 (0.0) | |
| **Multiorgan failure, n (%)** | 2 (2.4) | 2 (4.1) | 0 (0.0) | 0 (0.0) | |
| **Postoperative liver failure, n (%)** | 8 (9.5) | 6 (12.2) | 1 (3.6) | 1 (14.3) | |
| **Pulmonary embolism, n (%)** | 1 (1.2) | 1 (2.0) | 0 (0.0) | 0 (0.0) | |
| **IVC injury, n (%)** | 1 (1.2) | 1 (2.0) | 0 (0.0) | 0 (0.0) | |
| **Perioperative mortality, n (%)** | 7 (8.3) | 2 (4.1) | 4 (14.3) | 1 (14.3) | 0.21 |
| **Estimated blood loss (CC), (Mean ± SD)** | 1,071.59 ± 933.03 | 1,126.33 ± 982.87 | 964.89 ± 851.47 | 1,100 ± 975.11 | 0.77 |
| **Operative time (Min), (Mean ± SD)** | 315.12 ± 118.11 | 301.42 ± 108.91 | 311.85 ± 115.53 | 423 ± 150.35 | 0.03* |
| **Median survival (month)** | 16.8 | 23.2 | 9.2 | 16.5 | < 0.001* |

**P*-value less than 0.05 was statistically significant

The study investigated overall survival duration in all cholangiocarcinoma patients who received surgical treatment. The overall median survival duration was found to be 16.8 months. When comparing median survival durations among different locations of cholangiocarcinoma, it was observed that the intrahepatic type had the highest median survival at 23.2 months, followed by the distal type at 16.5 months and the perihilar type at 9.2 months. These differences were statistically significant ($p$-value < 0.01), as shown in Figure 1.

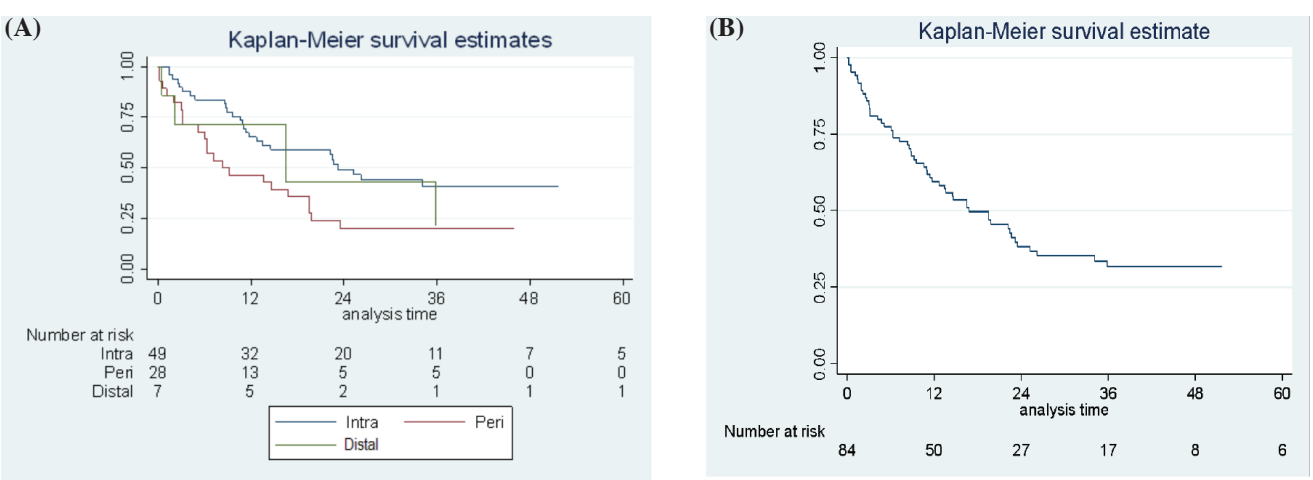


**Figure 1** Overall survival for the entire group (A) and by tumor location (B)

The study also examined the impact of surgical outcomes, including positive surgical margins, lymph node involvement, tumor size, and degree of differentiation on survival outcomes. It was found that positive surgical margins and lymph node involvement had a significant impact on survival, with adjusted hazard ratios of 2.19 (95% CI 1.24-3.83) and 1.85 (95% CI 1.07-3.23), respectively, as shown in Figure 2 and Table 4.

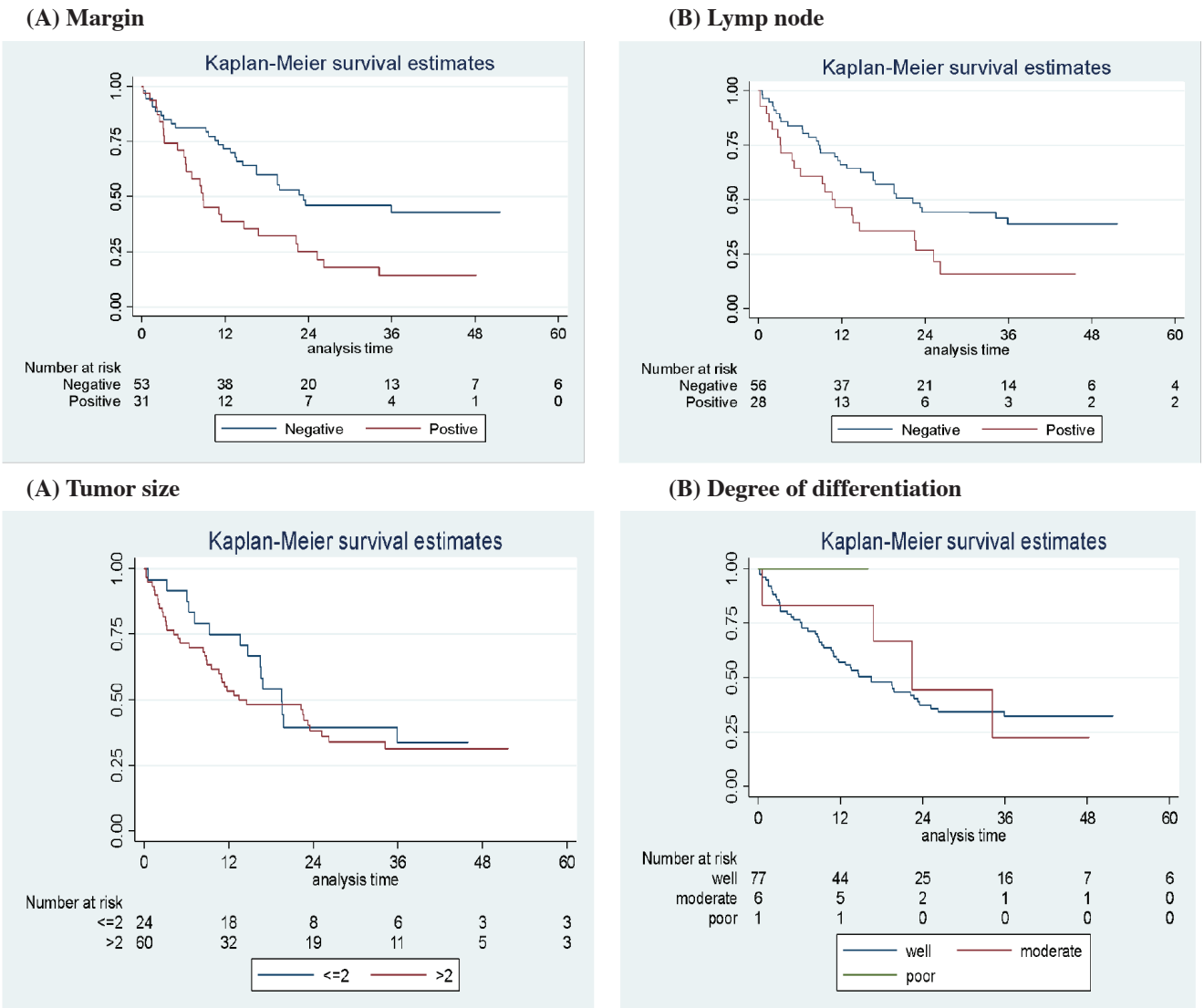


**Figure 2** Survival by margin (A), lymph node (B), tumor size (C) and degree of differentiation (D)

**Table 4** Factors predicting survival by tumor location

| Factors | Overall | | Intrahepatic | | Perihilar | | Distal | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Margin** | | | | | | | | |
| Negative | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Positive | 2.20 (1.29 - 3.77)* | 2.19 (1.24 - 3.83)* | 2.42 (1.22 - 5.23)* | 1.94 (0.80 – 4.70) | 1.51 (0.62 – 3.65) | 3.74 (0.34 – 2.40) | 5.47 (0.31 - 87.82) | NA |
| **Lymph node** | | | | | | | | |
| Negative | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Positive | 1.90 (1.10 - 3.29)* | 1.85 (1.07 - 3.23)* | 2.97 (1.37 - 6.43)* | 2.87 (1.25 - 6.58)* | 2.29 (0.94 - 5.57) | 3.74 (1.31 - 10.69)* | NA | NA |
| **Tumor size** | | | | | | | | |
| ≤ 2 cm | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| > 2 cm | 1.23 (0.67 - 2.23) | 1.24 (0.68 - 2.28) | NA | NA | 1.71 (0.73 - 4.01) | 2.90 (1.01 - 8.35)* | NA | NA |
| **Differentiation** | | | | | | | | |
| Well | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Moderate | 0.87 (0.32 - 2.41) | 0.55 (1.91 - 1.57) | 0.81 (0.19 - 3.45)* | 0.43 (0.09 - 2.07) | 1.91 (0.44 - 8.37) | 4.63 (0.79 - 26.99) | NA | NA |
| Poor | NA | NA | NA | NA | NA | NA | NA | NA |

**P*-value less than 0.05 was statistically significant

## Discussion

From the research study, a total of 84 cholangiocarcinoma patients who underwent surgery and had confirmed pathological specimens at Khon Kaen Hospital over a 5-year period, from 2014 to 2019, were included. These patients were categorized into three groups based on the location of the tumor: intrahepatic, perihilar, and distal cholangiocarcinoma.

It is noteworthy that most patients presented with abdominal pain and jaundice. In the clinical setting, perihilar type was observed most frequently. However, the proportion of patients in this study was different, with intrahepatic type being the most prevalent. This difference can be attributed to the higher likelihood of surgical treatment for the intrahepatic type compared to the perihilar type. This is because, from an anatomical perspective, the perihilar type is located in close proximity to critical structures and has a higher tendency to invade adjacent tissues, making it less amenable to surgical resection. Therefore, the opportunity for surgical treatment for the perihilar type is lower than for the intrahepatic type.

When statistically compared, the study observed that the group of perihilar type had the shortest overall survival time among the three groups: intrahepatic, perihilar, and distal type cholangiocarcinoma. This shorter survival duration in perihilar cholangiocarcinoma patients is significant and is attributed to various factors. Firstly, the negative margin achieved during surgery was 35.7%, the most limited in the perihilar type compared to the other two groups, 75.5% in the intrahepatic type and 85.7% in the distal type. This indicates that complete removal of cancerous tissue was less achievable in the perihilar type, which can negatively impact patient outcomes. Secondly, the higher incidence of angiolymphatic invasion in the perihilar type was 42.9% compared to the other two groups, 24.5% in the intrahepatic type and 14.1% in the distal type. Angiolymphatic invasion is a negative prognostic factor associated with a more aggressive disease course. Additionally, the study showed the presence of overall lymph node involvement at 33.3%, indicating that

cancer had spread to the lymph nodes during the surgical treatment. This lymph node involvement is associated with a worse prognosis and reduced survival time.

Overall, these findings highlight the complex nature of cholangiocarcinoma and the challenges associated with its treatment. The limited feasibility of achieving negative margins, the higher likelihood of lymph node involvement, and the presence of angiolymphatic invasion contribute to the shorter survival times observed in cholangiocarcinoma patients. These results are consistent with previous research, further emphasizing the importance of accurate prognostic factors in guiding treatment decisions for cholangiocarcinoma patients.

From the study, it is evident that the treatment of perihilar cholangiocarcinoma had the lowest rate of achieving negative margins when compared to intrahepatic and distal extrahepatic cholangiocarcinoma groups, requires a more extensive surgical approach involving the removal of liver tissue in addition to the tumor itself is attributed to the anatomical location of the tumor which is often situated close to critical structures and can easily spread to adjacent tissues and to achieve negative margins effectively. This extensive surgical procedure is associated with a higher risk of complications and mortality compared to intrahepatic and distal cholangiocarcinoma cases. As a result, complete tumor removal through surgery is more challenging in perihilar cholangiocarcinoma.

It is widely known that intrahepatic cholangiocarcinoma has a different epidemiology than extrahepatic cholangiocarcinoma. Our study observed that patients with intrahepatic cholangiocarcinoma had the best overall survival outcomes among the three groups, even though there was a lower rate of R0 resection and a higher incidence of metastasis to the lymph nodes compared to distal types. This finding is consistent with some previous research.[8,9]

The preoperative assessment of patients with cholangiocarcinoma has evolved significantly in recent years. The goal is to obtain the most accurate and detailed information to ensure precise surgical planning. Advanced imaging techniques are now commonly used in the evaluation process, including high-resolution computed tomography (CT) scans that can create three-dimensional reconstructions. Additionally, computerized tomography angiography (CTA) of the visceral organs and magnetic resonance cholangiopancreatography (MRCP) is employed to visualize the biliary tract and liver.[11]

## Conclusion

The surgical treatment of cholangiocarcinoma at Khon Kaen Hospital has demonstrated favorable treatment outcomes, high safety levels, minimal complications, and a low mortality rate following surgery. These results align with the standards observed in other research studies. Key factors associated with long-term survival include achieving R0 resection and the absence of lymph node involvement. As a result, there is a strong focus on developing surgical techniques that optimize R0 resection and the early detection of patients who do not yet display signs of lymph node spread. Continuous research efforts in this direction are ongoing at Khon Kaen Hospital.

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