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Original Article

Practice guidelines for managing extrahepatic biliary tract cancers

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Backgrounds/Aims: Reported incidence of extrahepatic bile duct cancer is higher in Asians than in Western populations. Korea, in particular, is one of the countries with the highest incidence rates of extrahepatic bile duct cancer in the world. Although research and innovative therapeutic modalities for extrahepatic bile duct cancer are emerging, clinical guidelines are currently unavailable in Korea. The Korean Society of Hepato-Biliary-Pancreatic Surgery in collaboration with related societies (Korean Pancreatic and Biliary Surgery Society, Korean Society of Abdominal Radiology, Korean Society of Medical Oncology, Korean Society of Radiation Oncology, Korean Society of Pathologists, and Korean Society of Nuclear Medicine) decided to establish clinical guideline for extrahepatic bile duct cancer in June 2021.
Methods: Contents of the guidelines were developed through subgroup meetings for each key question and a preliminary draft was finalized through a Clinical Guidelines Committee workshop.
Results: In November 2021, the finalized draft was presented for public scrutiny during a formal hearing.
Conclusions: The extrahepatic guideline committee believed that this guideline could be helpful in the treatment of patients.

Key Words: Extrahepatic; Bile duct cancer; Guidlines

INTRODUCTION

In recent years, the medical field has witnessed considerable advancements in therapeutic interventions, leading to commendable therapeutic outcomes. Such advancements are now disseminated globally to both medical professionals and the general public through esteemed academic publications and digital platforms.

The determination of a patient's therapeutic regimen should predominantly be anchored in the expertise and sagacity of presiding medical professionals, always taking into account individual patient profiles. Nevertheless, it is paramount to underscore the necessity of ensuring that the clinical judgement of these medical professioals is steeped in principles of 'evidence-based medicine,' especially given the profound information available. Every patient, irrespective of the attending physician's level of experience, is essentially entitled to a consistent standard of treatment decision. Therefore, efforts to provide standardized clinical recommendations based on results of evidence-based medicine for specific diseases and collective experience of medical professionals are taking place worldwide.

In alignment with this global endeavor, the Korean Society of

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Hepato-Biliary-Pancreatic Surgery took the initiative to formulate the 'Extrahepatic Bile Duct Cancer Treatment Guidelines' in 2021, marking a pioneering effort in the Republic of Korea.

Extrahepatic bile duct cancer has been reported to have a higher incidence in Asians than in Western populations. Korea, in particular, is one of the countries with the highest incidence rates of extrahepatic bile duct cancer in the world, ranking second among men and third among women. Although burgeoning research and innovative therapeutic methodologies are emerging both domestically and internationally, there remains a palpable void in clinical guidelines tailored specifically to the unique epidemiological landscape of the Republic of Korea.

In light of this, under the leadership of the Korean Society of Hepato-Biliary-Pancreatic Surgery, preeminent experts in the field of extrahepatic bile duct cancer have convened to furnish the medical community with the most up-to-date and accurate information pertaining to the diagnosis and therapeutic management of extrahepatic bile duct cancer.

MATERIALS AND METHODS

Development process of clinical guidelines

The Korean Society of Hepato-Biliary-Pancreatic Surgery in collaboration with related societies (Korean Pancreatic and Biliary Surgery Society, Korean Society of Abdominal Radiology, Korean Society of Medical Oncology, Korean Society of Radiation Oncology, Korean Society of Pathologists, and Korean Society of Nuclear Medicine) decided to establish clinical guidelines for extrahepatic bile duct cancer in June 2021. Each respective society undertook the task of delineating key questions and proceeded with a meticulous examination of literature pertinent to those questions. Subsequent to this endeavor, a comprehensive reference document was synthesized. Accumulated literature was systematically categorized according to its topic, with each piece being ascribed an evidence-based designation. Contents of guidelines were developed through subgroup meetings for each key question. A preliminary draft was finalized through a Clinical Guidelines Committee workshop. In November 2021, the finalized draft was presented for public scrutiny during a formal hearing.

Literature search

Literature search was conducted by focusing on keywords for each key question selected by the Clinical Practice Guideline Development Committee. Major domestic and international databases, including Ovid-Medline, Ovid-Embase, Cochrane Library, and KoreaMed, were used for the search. There was no restriction on publication year. The search was completed in December 2021. For papers published after December 2021, their contents were supplemented as much as possible with descriptive information.

The search strategy was methodically constructed with the assistance of methodology experts to enhance sensitivity, utilizing only 'P' and 'I' components of PICO (Patient, Intervention, Comparison, Outcome). Both domestic and international databases were utilized to ensure that the final guideline could reflect the domestic situation [1,2].

The final selection process for the identified literature required clinical expertise. Thus, each Clinical Practice Guideline Development Committee conducted. Selection criteria for

Table 1. Definition of the level of evidence

Sign	Level of evidence	Definition
I	High	• Research design: • (Intervention) These are the results obtained from randomized controlled trials or comparative group observational studies. • (Diagnosis) These are the results obtained from randomized controlled trials or diagnostic accuracy studies in the form of cross-sectional cohorts. • Considerations: There are no methodological concerns in the quality assessment of the evidence, and the evidence is consistent and precise, ensuring high reliability of the synthesized results.
II	Moderate	• Research design: • (Intervention) These are the results obtained from randomized controlled trials or comparative group observational studies. • (Diagnosis) These are the results obtained from randomized controlled trials or cross-sectional cohort diagnostic accuracy studies. • There are slight concerns regarding the quality assessment of the evidence, the consistency of the evidence, or the precision of the evidence, resulting in a moderate level of confidence in the synthesized results.
III	Low	• Research design: • (Intervention) These are the results obtained from observational studies with or without a control group. • (Diagnosis) These are the results obtained from diagnostic accuracy studies with a patient-control group design.
IV	Very low	• Research design: • (Intervention) These are composed of observational studies without a control group or expert opinions, reviews, and the like. • (Diagnosis) These are the results obtained from diagnostic accuracy studies with a patient-control group design. • Considerations: There are very serious concerns regarding the quality assessment of the evidence, the consistency of the evidence, or the precision of the evidence, resulting in very low confidence in the synthesized results.

the literature were established according to key questions. A two-stage selection/exclusion process was carried out. Two independent reviewers conducted the review for each individual paper. Reasons for exclusion were documented. In cases where there were disagreements between reviewers in both selection processes, a consensus process was undertaken to reach a final decision [3-5].

Determining the level of evidence and recommendation grades

We determined the level of evidence and recommendation grades for each key question. The level of evidence was determined with a four-tier system based on a thorough review of major foreign methodologies such as the Scottish Intercollegiate Guidelines Network (SIGN) [6] and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [7-11] as well as existing domestic clinical treatment guidelines. The development committee discussed and modified the existing GRADE system to create a new system as shown in Table 1.

When assessing the level of evidence, research design and quality assessment of the selected literature literature were given top priority. Additionally, the relevance of results and the precision of evidence (including total number of subjects and confidence interval [CI] of the included literature) were considered. These factors were taken into account when determining the level of evidence for each key question.

We categorized recommendation grades into four levels: strong recommendation, conditional recommendation, not recommended, and inconclusive (Table 2). The decision on recommendation grade took into account several factors, including the level of evidence, benefits, harms, clinical applicability (resource and cost), value, and preference.

RESULTS

Resecatble extrahepatic cholangiocarcinoma

KQ1. In patients with suspected extrahepatic bile duct cancer where curative surgery is deemed possible, preoperative tissue examination or cytological diagnosis is selectively considered.

Recommendation grade	B. Conditional recommendation
Level of evidence	IV. Very low

In a study involving 250 patients who underwent liver resections for suspected malignant lesions, a mere 7.2% received a positive diagnosis postsurgery. In a cohort of 41 patients suspected of having hilar cholangiocarcinoma, 10 (24.4%) were identified as false positives [12]. This denotes a significantly elevated incidence of false positives within this subcategory. Another study published in 2016 surveying a similar cohort of 250 patients undergoing surgical procedures on the suspicion of hilar cholangiocarcinoma identified 34 (13.6%) who was positively diagnosed during the preoperative phase. Intriguingly, amongst this subset, 10 individuals could have potentially circumvented surgical intervention had there been a more comprehensive preoperative tissue examination or an exploratory surgical procedure. Yet, for the remaining 24 positively diagnosed patients, surgical means were a solitary avenue for an unequivocal malignancy confirmation given inherent diagnostic complexities [13].

When patients exhibit ambiguous indications of biliary obstruction in diagnostic imaging, the sensitivity of brush cytology and bile duct cytological examination facilitated through endoscopic retrograde cholangiopancreatography (ERCP) ranged from 27% to 81%, demonstrating variability across distinct studies [14]. For infiltrative cholangiocarcinoma, the most common type, the efficacy of procuring tissue sample is generally low, rendering the endeavor of preoperative tissue validation exceedingly intricate. The propensity for false negatives is also disconcertingly elevated, which not only impedes the definitive exclusion of malignancy, but also inadvertently prolongs the imperative for surgical interventions. Apart from ERCP as a preoperative diagnostic test, endoscopic ultrasound-fine needle aspiration (EUS-FNA) cytology diagnosis is still an area with limited research. Generally, when performing tissue sampling via ERCP, complications related to the ERCP procedure, such as pancreatitis, cholangitis, and cholecystitis, can occur. A 2017 study involving 210 patients diagnosed with

Table 2. Definition of strength of recommendation

Sign	Strength of recommendation	Definition
A	Strong recommendation	Strong recommendation is made for most clinical situations when the benefits of the intervention/test outweigh the risks, considering the level of evidence, values and preferences, and resources.
B	Conditional recommendation	The use of this intervention/test may vary depending on the clinical situation or patient/social values, so it is recommended to use it selectively or conditionally.
C	Not recommendation	The potential harms of this intervention/test may be greater than the benefits, and considering the clinical situation or patient/social values, it is recommended not to implement it.
D	Inconclusive	When considering the benefits and harms of this intervention/test, the level of evidence is too low, and the balance between benefits and harms is seriously uncertain or there is significant variability. Therefore, the decision to implement the intervention is not determined.

malignant biliary obstruction reported that the complication rate and mortality rate associated with ERCP were 8.9% and 1.3%, respectively [15]. Another 2017 comparative study showed that both overall and disease-free survival rates were significantly decreased for cholangiocarcinoma patients with biliary inflammation (p = 0.022 and p = 0.007, respectively). Biliary inflammation was considered a pivotal prognostic indicator for extrahepatic cholangiocarcinoma patients regardless of its severity [16]. For patients requiring biliary drainage as a preoperative treatment due to biliary obstruction, it is challenging to directly associate an elevated risk of complications, notably cholangitis, with additional tissue sampling performed during ERCP drainage procedures. In 2015, expert opinions and two review studies in 2019 and 2012 suggested that a preoperative histopathological examination might not be essential for those with suspected extrahepatic cholangiocarcinoma if imaging studies had already ruled out a positive diagnosis and if surgical intervention remained a viable option [17-19]. However, it merits emphasis that existing research on the necessity for preoperative histopathological diagnosis largely relies on retrospective, non-randomized studies. The lack of controlled studies rigorously assessing performances of histological examinations casts certain reservations on the integrity of prevailing evidence in this particular field.

Current research has yet to conclusively determine the safety of extra tissue sampling during ERCP drainage procedures in some patients. Similarly, the effectiveness of cholangioscopy for examining tissues in patients with hilar cholangiocarcinoma remains unclear. Consequently, when considering patients for curative surgery based on non-invasive diagnostics, decisions regarding preoperative tissue examinations can be considered selectively with interdisciplinary discussions.

KQ2. CA19-9 testing is performed on patients suspected of having extrahepatic bile duct cancer.

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

In patients suspected of having extrahepatic cholangiocarcinoma, CA19-9 testing can be performed. Given the relatively poor prognosis associated with extrahepatic cholangiocarcinoma, early detection of cancer is essential for treatment and prognosis. Efforts have been made to develop markers useful for the diagnosis of extrahepatic cholangiocarcinoma, with CA19-9 being one of the most well-known and widely practiced markers. Extensive research has been performed on its utility.

Multiple studies have investigated the usefulness of CA19-9 testing in the diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis, with varying thresholds for CA19-9 in different studies. While its sensitivities ranged from 53% to 75% across studies, its specificities were notably high, ranging from 67% to 97.7%. However, most of these studies were retrospective. It is known that combining CA19-9 testing with other diagnostic measures such as cytology and tissue examination can improve its sensitivity and specificity [20,21].

One randomized clinical trial monitoring 75 primary sclerosing cholangitis patients for three years employed CA19-9 testing every 6 months along with three other tumor markers. In this study, two patients developed cholangiocarcinoma. Of them, one had normal tumor marker level while the other had an increased level. Twenty-one patients had an increase in at least one marker at least once and five patients had a transient increase of more than double the upper limit of normal for tumor markers. This study suggests that CA19-9 testing has limited value in asymptomatic patients with primary sclerosing cholangitis [22].

One study has also investigated the use of CA19-9 testing before performing a liver transplant in patients with primary sclerosing cholangitis to check for the presence of cholangiocarcinoma. In that study, 12 out of 26 patients had CA19-9 levels more than twice the laboratory reference range and two of them had cholangiocarcinoma. However, among the 14 patients with normal levels, two were diagnosed with cholangiocarcinoma. There was no correlation between CA19-9 elevation and biliary dysplasia in that study [23]. These results underscored the complexity of relying solely on CA19-9 levels.

There were two prospective studies involving patients with bile duct obstruction, excluding those with primary sclerosing cholangitis. One study reported that when using a threshold of 35 kU/L for CA19-9, its sensitivity and specificity were 77.9% and 76.3%, respectively. When the threshold was increased to 100 kU/L, its sensitivity and specificity were 67.5% and 86.8%, respectively. This suggests that raising the threshold decreases the sensitivity while increasing the specificity [24]. In another study that used a threshold of 100 U/mL, CA19-9 demonstrated a sensitivity of 75% and a specificity of 80% [25]. CA19-9 testing appears to have potential utility in differentiating between cholangiocarcinoma and benign strictures in patients with bile duct obstruction, even when primary sclerosing cholangitis is not present. In a study involving 115 patients with hilar cholangiocarcinoma, 47 patients with cholangitis, and 65 healthy control subjects, CA19-9 testing had a sensitivity of 65.2% and a specificity of 87.5%, somewhat inferior to exosomal Cripto-1 [26]. In another study involving 250 patients suspected of having hilar cholangiocarcinoma, 34 (13.6%) patients were ultimately diagnosed with a positive condition. When CA19-9 serum levels were above 61.2 U/mL, the sensitivity, specificity, and diagnostic accuracy for predicting cholangiocarcinoma were 74.6%, 80.0%, and 83.5%, respectively. Based on these results, that study reported that with additional tests and exploratory surgery, 10 out of the 34 patients with positive conditions were able to avoid surgery [13].

A meta-analysis of a total of 31 studies involving 1,264 patients with bile duct cancer and 2,039 control subjects has been

conducted. A sensitivity of 0.72 (95% CI: 0.70–0.75), a specificity of 0.84 (95% CI: 0.82–0.85), a positive likelihood ratio of 4.93 (95% CI: 3.67–6.64), a negative likelihood ratio of 0.35 (95% CI: 0.30–0.41), and a diagnostic odds ratio [OR] of 15.10 (95% CI: 10.70–21.32) were reported for CA19-9 testing. The area under the summary receiver operating characteristic (SROC) curve was 0.8300. The accuracy of CA19-9 testing was influenced by the control group, geographical location, and sample size. While there was a consistent trend in diagnostic accuracy based on control group type, studies involving European patients and small sample sizes reported lower sensitivities [27]. In a systematic review of a single marker for cholangiocarcinoma encompassing 46 papers, CA19-9 and carcinoembryonic antigen (CEA) tests were reported to have sensitivities ranging from 47.2% to 98.2% and specificities ranging from 89.7% to 100% [28].

Generally, CA19-9 testing is reported to have higher sensitivity and specificity for cholangiocarcinoma than CEA testing. However, in some studies, CEA testing has been reported as superior. In a study involving 190 patients, CEA was found to be more accurate than CA19-9 testing in distinguishing between patients with primary sclerosing cholangitis and those with cholangitis. Multivariate analysis indicated that CEA was an independent predictor of survival [29]. Recent research efforts have been directed toward finding markers superior to CA19-9, using a combination of tests to improve diagnostic accuracy compared to CA19-9 testing alone and exploring ways to enhance the overall accuracy of diagnosis.

In studies utilizing various markers such as DNA methylation markers [30], neutrophil gelatinase-associated lipocalin (NGAL) [31], microRNA-150 [32], Resolvin D1 [33], matrix metalloproteinase-7 (MMP7) [34], circulating cell-free DNA [35], glycobiomarkers [36] like CA19-9, Wisteria floribunda agglutinin (WFA), anti-sialylated mucin 1 (MUC1) [37], interleukin 6 [38], and B7-H4 [39] in bile, CA19-9 testing demonstrated results that were similar to or slightly inferior to other markers. Combining these tests with CA19-9 testing was proven to be more helpful in differentiating between cholangiocarcinoma and benign biliary strictures than using CA19-9 alone sometimes.

Besides its diagnostic utility, CA19-9 testing holds predictive value for extrahepatic cholangiocarcinoma prognosis. In one study, a total of 143 patients with elevated preoperative serum CA19-9 levels were classified into normalizing and non-normalizing groups (postoperative early serum CA19-9 ≤ 37 and > 37 U/mL). The rise in CA19-9 was found to be a significant independent predictor of poor prognosis in multivariate analysis, helping identify patients who required additional treatment and close monitoring [40]. In another study, 2,100 extrahepatic cholangiocarcinoma patients were divided into normal (n = 626, 32%) and elevated (n = 1,474, 68%) groups based on CA19-9 > 38 U/mL. The median overall survival was lower in the CA19-9 elevation group (8.5 months vs. 16 months, $p < 0.01$). Multivariate analysis demonstrated that CA19-9 elevation was independently associated with a worse prognosis (hazard ratio [HR]: 1.72, 95% CI: 1.46–2.02, $p < 0.01$) [41]. In a cohort study involving 486 patients who underwent surgery for Klatskin tumors, preoperative CA19-9 levels were found to be helpful in predicting early recurrence in multivariate analysis [42]. Even in the treatment of perihilar cholangiocarcinoma, tumor stage, resectability, and survival rates were found to be correlated with preoperative CA19-9 and CEA serum levels. Patients with preoperative serum levels of CA19-9 > 1,000 U/mL and CEA > 14.4 ng/mL had significantly lower resection rates and survival rates than those with lower CA19-9 and CEA serum levels [43]. In another study, overexpression of markers for cancer stem cells, when combined with CA19-9 test results, was found to be helpful for predicting recurrence after treatment [44].

KQ3. In cases where imaging studies reveal unexplained bile duct strictures or dilation, additional endoscopic diagnostic procedures such as endoscopic ultrasound (EUS) may be considered for further differential diagnosis.

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

There were five prospective studies [45-49], two retrospective studies [50,51], and a literature review [52] on the necessity of performing EUS for further differential diagnosis in patients with observed bile duct dilation through radiological imaging. In most of these studies, EUS was reported to be beneficial for further discerning the cause of bile duct dilation when standard imaging remained inconclusive. For instance, in a specific study concerning unexplained bile duct dilation detected by abdominal ultrasound, EUS was noted to have a sensitivity of 89.5%, a specificity of 100%, and an accuracy rate of 90.9% [49].

In a study of patients with extrahepatic bile duct strictures without observed masses on contrast-enhanced CT, EUS was performed to differentiate benign and malignant bile duct strictures. EUS showed a sensitivity of 94.1%, a specificity of 82.3%, and an accuracy of 88.2% in discriminating bile duct strictures, suggesting its utility [51]. For the diagnosis of malignant tumors in patients with bile duct dilation, EUS (sensitivity: 100%, specificity: 100%, accuracy: 95%) was reported to be a valuable test, with a diagnostic accuracy similar to magnetic resonance cholangiopancreatography (MRCP) (sensitivity: 95%, specificity: 98%, accuracy: 97%) [46]. Based on these research findings, EUS is considered useful for additional differential diagnosis in cases of unexplained bile duct dilation or bile duct strictures observed through imaging studies.

The utility of EUS-FNA for the diagnosis of bile duct strictures suspected of cholangiocarcinoma was evaluated in three prospective studies [53-55], one retrospective study [56], and one systematic literature review with meta-analysis. It was reported that EUS-FNA could be helpful in diagnosing chol-

angiocarcinoma in cases where cytology-based diagnosis had failed in patients with suspected malignant bile duct strictures.

In a study that directly compared tissue acquisition through EUS-FNA and ERCP in patients with suspected malignant bile duct obstruction, tissue acquisition through EUS-FNA (with a sensitivity of 94% and accuracy of 94%) was statistically superior to ERCP (with a sensitivity of 50% and accuracy of 53%). Nevertheless, this study included cases of pancreatic cancer and restricted its direct relevance to cholangiocarcinoma. A subgroup analysis within that study showed that for bile duct masses, both methods had a similar sensitivity of 79%. For cases of unclear biliary strictures, the sensitivity was 80% for EUS-FNA and 67% for ERCP, showing no significant difference between the two.

A meta-analysis of six studies involving 196 patients with biliary strictures showed a sensitivity of 66% and a negative likelihood ratio of 0.34 for EUS-FNA, which was reported to be useful for diagnosing cholangiocarcinoma in patients with biliary strictures [57].

However, it is important to note that EUS-FNA can carry risks related to the procedure, such as complications and seeding through the needle tract. In addition, its success may depend on the operator's expertise. Therefore, it is recommended to use EUS-FNA in a limited manner as part of a multidisciplinary approach when cytological diagnosis has failed in cases of suspected malignant bile duct strictures.

There were eight prospective studies [58-65] and one retrospective study [66] on the utility of intraductal ultrasound (IDUS) for the diagnosis of bile duct strictures suspected of cholangiocarcinoma. It has been reported that IDUS can improve the accuracy of tissue diagnosis in cases of unclear biliary strictures, assist in staging based on bile duct wall invasion, and help determine the extent of tumor involvement within the bile duct to assess resectability.

In a study that compared the diagnostic accuracy between patients with suspected malignant bile duct strictures who underwent tissue sampling through ERCP alone and those who had tissue sampling guided by IDUS, the diagnostic accuracy was reported to be 73% for ERCP and 100% for ERCP + IDUS [61]. Using IDUS significantly improved the diagnostic accuracy of malignant bile duct strictures. Various other studies [60,65,66] have reported that the diagnostic accuracy for IDUS ranges from 83% to 92%. Furthermore, IDUS has been found to be useful for distinguishing ampullary tumors within the bile duct and in the setting of T-staging based on bile duct wall invasion.

Additionally, for determining the extent of intraductal involvement in hilar cholangiocarcinoma, studies have reported diagnostic accuracies of preoperative methods including computerized tomography (CT) (66.6%–80%), MRCP (84.2%), ERCP (43%–60%), and IDUS (84%–100%), which can be helpful for predicting resectability.

In cases where a precise diagnosis is challenging with conventional imaging studies or ERCP, endoscopic examination of the bile duct can be performed. It can also be used for confirming the extent of specific conditions such as bile duct strictures or cholangiocarcinoma. Currently, available methods for bile duct endoscopy include the mother-baby endoscope system, the SpyGlass system (SpyGlass Direct Visualization System), and direct peroral cholangioscopy (direct POC) with the use of ultra-slim endoscopes [67].

KQ4. Is preoperative biliary drainage useful in resectable extrahepatic cholangiocarcinoma?

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

Research on the necessity of biliary drainage in patients with extrahepatic cholangiocarcinoma can be categorized based on the location of the tumor, such as hilar cholangiocarcinoma and distal cholangiocarcinoma. Many studies have focused on patients with hilar cholangiocarcinoma. Most studies that included patients with distal cholangiocarcinoma primarily targeted periampullary neoplasms, including pancreatic cancer, duodenal cancer, and periampullary cancers might be resectable. Therefore, there is limited evidence to evaluate the necessity of preoperative biliary drainage in distal cholangiocarcinoma cases that are resectable.

In a systematic literature review and meta-analysis of three papers focusing on patients with resectable hilar cholangiocarcinoma, preoperative biliary drainage showed no significant difference in postoperative mortality or in-hospital mortality compared to the group without this procedure. However, they did observe an increase in morbidity. Specifically, in 16 retrospective comparative studies analyzed by Teng et al. [68], the group that underwent biliary drainage showed higher morbidity rate (OR: 0.67, 95% CI: 0.53 to 0.85, $p = 0.0009$), intraoperative blood transfusion (OR: 0.72, 95% CI: 0.55 to 0.94, $p = 0.02$), bile leak (OR: 0.58, 95% CI: 0.24 to 1.41, $p = 0.04$), infection (OR: 0.31, 95% CI: 0.20 to 0.47, $p < 0.00001$), and cholangitis (OR: 0.18, 95% CI: 0.007 to 0.48, $p = 0.0007$). Conversely, the group that did not undergo biliary drainage showed a higher rate of liver failure (OR: 3.09, 95% CI: 1.15 to 8.31, $p = 0.03$). Mehrabi et al. [69] analyzed 16 retrospective comparative studies and reported that while there was no significant relationship between biliary drainage and mortality, the group that underwent biliary drainage had a higher morbidity rate (OR: 1.51, 95% CI: 1.14 to 2.00, $p = 0.002$) and cancer recurrence rate (OR: 2.07, 95% CI: 1.38 to 3.11, $p = 0.003$). In patients who met appropriate selection criteria, biliary drainage resulted in lower morbidity rates (OR: 0.51, 95% CI: 0.18 to 1.42, $p = 0.03$) compared to those without drainage. In another analysis of nine retrospective comparative studies conducted by Celotti et al. [70], no significant relationship was found between biliary drainage and mortality. However, the group that underwent

biliary drainage had higher morbidity rate (relative risk [RR]: 1.266, 95% CI: 1.039 to 1.543, $p = 0.011$) and wound infection (RR: 2.035, 95% CI: 1.041 to 3.977, $p = 0.038$).

However, this tends to contradict results observed in individual studies. In most studies, there was no statistically significant difference in mortality or morbidity rate between the group that underwent biliary drainage and the group that did not. Kimura et al. [71] reported a significantly reduced 5-year survival rate in the group that underwent biliary drainage compared to the group that did not (RR: 2.21, 95% CI: 1.14 to 4.27, $p = 0.018$). El-Hanafy [72] reported a higher morbidity rate in the group that underwent biliary drainage compared to the group that did not (58.6% vs. 20.3%, $p = 0.001$). On the other hand, Farges et al. [73] found no difference in mortality rate between the group that underwent biliary drainage and the group that did not. Still, they noted that biliary drainage reduced mortality rate of patients who underwent hepatic lobectomy (adjusted OR: 0.29, 95% CI: 0.11 to 0.77, $p = 0.013$) while increasing the mortality rate of patients who underwent hepatic segmentectomy (adjusted OR: 4.06, 95% CI: 1.01 to 16.30, $p = 0.035$). Some studies did not show significant differences between the group that underwent biliary drainage and the group that did not [74-80]. However, biliary drainage was associated with an increase in complications [81-83], longer hospital stays [81,84,85], and side effects such as tumor dissemination or seeding [71,86].

In summary, biliary drainage in general did not reduce mortality or morbidity rate. It could sometimes lead to procedure-related side effects. Nonetheless, several studies found that it was effective in selective cases, such as when future liver remnant (FLR) was less than 30% [87] or in right hepatectomy procedures [73,88]. Additionally, although benefits of biliary drainage itself were insignificant, factors related to the purpose of the procedure, such as inadequate drainage [89] due to preoperative cholangitis [89], FLR less than 50%, and resolution of jaundice, had significant effects on mortality and morbidity rates.

Furthermore, elevated serum bilirubin levels were often associated with increased mortality and postoperative complications, although the specific threshold for bilirubin level varied between studies [73,76,78,84,90-92].

Biliary drainage methods encompass endoscopic and percutaneous approaches. Endoscopic methods include endoscopic nasobiliary drainage (ENBD), endoscopic retrograde biliary drainage (ERBD), and self-expanding metal stents (SEMS). Percutaneous methods involve percutaneous transhepatic biliary drainage (PTBD). Many existing studies feature a mix of these methods. However, criteria for selecting these techniques are not well-established, emphasizing the need for further research. When applying these methods in a clinical setting, individual patient status and available resources should be taken into account.

One limitation of previous research was that most studies were retrospective and not randomized, which could introduce inherent drawbacks. Many studies had imbalanced proportions between groups that underwent biliary drainage and those that did not. Additionally, while several studies were conducted across multiple institutions, sample sizes in these studies were often small. To establish a higher level of evidence for recommendations, controlled prospective studies tailored to specific cases are necessary.

KQ5. Criteria for distinguishing perihilar (hilar) cholangiocarcinoma (Klatskin tumor) from distal cholangiocarcinoma are based on the anatomical definition of the common bile duct's (CBD's) insertion site of the cystic duct.

Recommendation grade	A. Strong recommendation
Level of evidence	III. Low

This distinction is made by collectively referring to the left and right intrahepatic bile ducts and their confluence into the third branch as "perihilar" or "hilar" cholangiocarcinoma. The extrahepatic bile duct is further divided into proximal CBD (from the confluence of left and right hepatic ducts to the insertion of the cystic duct) and distal CBD (from the insertion of the cystic duct to the ampulla of Vater) [93-95].

Variations in the insertion site of the cystic duct can lead to changes in relative lengths of the CBD and the extrahepatic bile duct. It is known that in 51%–75% of cases, the insertion of the cystic duct is located at the mid-portion of the extrahepatic bile duct [95-97].

The criteria for distinguishing between perihilar (hilar) cholangiocarcinoma and distal cholangiocarcinoma, as agreed upon by the National Comprehensive Cancer Network (NCCN), American Joint Committee on Cancer (AJCC) guidelines and the Korean Society of Abdominal Radiology, are based on the insertion site of the cystic duct in the CBD.

KQ6. Patients suspected of having extrahepatic cholangiocarcinoma are recommended to undergo diagnostic tests, including dynamic contrast-enhanced CT or magnetic resonance imaging (MRI) with MRCP.

Recommendation grade	A. Strong recommendation
Level of evidence	III. Low

Studies assessing the diagnostic accuracy of imaging tests for extrahepatic cholangiocarcinoma are predominantly small-scale retrospective studies. Presently, comprehensive prospective analyses that compare relative efficacies of abdominal ultrasound, dynamic contrast-enhanced CT, and MRCP-based contrast-enhanced MRI tests show a conspicuous absence.

Most meta-analysis papers have reported diagnostic accuracy based on results from retrospective studies. One such meta-analysis was conducted by Ruys and colleagues [98]. They

evaluated 16 retrospective studies and deduced that CT showed a diagnostic accuracy of 86% (95% CI: 77%–92%) for delineating the longitudinal tumor extent of extrahepatic cholangiocarcinoma, while MRI showed an accuracy range of 71%–80% [98]. However, their meta-analysis did not conduct statistical comparisons between CT and MRI in terms of diagnostic accuracy. In a study conducted by Park and colleagues [99], diagnostic accuracies of dynamic contrast-enhanced CT and MRCP-based contrast-enhanced MRI tests for assessing longitudinal tumor extent in 27 patients with extrahepatic cholangiocarcinoma were compared. Dynamic contrast-enhanced CT exhibited a diagnostic accuracy ranging from 87.0% to 90.7%, while MRCP-based contrast-enhanced MRI showed an accuracy in the range of 85.1%–87.0%. There was no significant difference between the two imaging tests ($p > 0.05$) [99].

Given these collective insights from results of studies mentioned above, it can be concluded that dynamic contrast-enhanced CT and MRCP-based contrast-enhanced MRI provide a similar level of accuracy for detecting and diagnosing tumors in patients suspected of having extrahepatic cholangiocarcinoma. The selection of an appropriate imaging technique for patients suspected of having extrahepatic cholangiocarcinoma and studies related to the diagnostic accuracy are limited in number, with most being small-scale single-institution retrospective studies. Further well-designed studies are needed.

KQ7. What are the criteria for evaluating the extent of extrahepatic bile duct cancer in preoperative imaging examination?

7-1. In contrast-enhanced CT and MRI, irregular thickening of the bile duct wall with enhancement and expansion of the upper bile duct are indicative of invasion of extrahepatic bile duct cancer (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	II. Moderate

In cross-sectional images, bile duct cancer appears as a lesion that causes irregular thickening of the bile duct wall, luminal narrowing, luminal obliteration, and expansion of the upper bile duct due to infiltration and nonuniform fibrosis of the cancer. Cholangiography has confirmed these findings by showing marked constriction of the lumen and irregular luminal shape [98,100-104]. The bile duct wall invaded by bile duct cancer enhances better in comparison with adjacent liver parenchyma in both arterial and portal phase. As time progresses, the enhancement of fibrotic tissue becomes more pronounced [105,106]. In comparison with benign strictures, extrahepatic bile duct cancer exhibits a thicker bile duct wall, a longer extent of the involved duct, and an irregular lumen [107-110]. When these imaging characteristics were combined in retrospective studies, they identified malignant strictures with an accuracy of 100% and benign strictures with an accuracy of 87% [109]. However, various benign inflammatory conditions such as postinflammatory fibrotic strictures, primary sclerosing cholangitis, immunoglobulin G4-related sclerosing cholangitis, recurrent suppurative cholangitis, and ischemic cholangitis can also mimic similar imaging findings. Therefore, differentiating between bile duct cancer and benign strictures is often challenging based solely on imaging, with bile duct tissue examination being necessary for diagnosis.

7-2. Description of the extent of axial invasion of hilar cholangiocarcinoma in preoperative CT and MRI follows the Bisthmus classification (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	IV. Very low

7-3. Assessment of expected boundaries of extrahepatic bile duct cancer in preoperative CT and MRI involves evaluating proximal and distal limits of the tumor (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	IV. Very low

The Modified Bisthmus-Corlette classification is widely used to describe the axial extent of extrahepatic bile duct cancer [111,112]. The Bisthmus-Corlette classification defines the extent of bile duct cancer based on involvement of primary branches of the bile duct and secondary branches of left and right intrahepatic bile ducts. It is useful for estimating surgical extent [111,113]. However, it is important to be cautious as the surgical extent based on the Bisthmus-Corlette classification may vary when there are variations in the bile duct system [112,113]. In addition, information about expected boundaries of the lesion is crucial for determining the surgical extent. Boundaries of the proximal part of the intrahepatic bile duct and the distal part of the extrahepatic bile duct should be evaluated based on the pancreas and described to determine whether additional pancreaticoduodenectomy is required [98].

In retrospective studies, the accuracy of contrast-enhanced CT for predicting the axial invasion range of extrahepatic bile duct cancer ranged from 75% to 96% [98,100,114-116], with a meta-analysis showing an accuracy of 86% [63,117,118]. The accuracy of MRCP was 71%–80%. When combined with contrast-enhanced MRI, the accuracy was improved to 87%–93.3% [63,114]. It is essential to exercise caution when evaluating the extent of axial invasion in images, as it can lead to underestimation of the extent. Tumors infiltrating along the mucosa or submucosa may not be detectable with current imaging examinations and this reason in need for the discovery of cancer during resection surgery [98,113].

KQ8. In preoperative CT or MRI examinations of patients with extrahepatic bile duct cancer, assessment of vascular in-

vasion is based on the degree of vascular occlusion, presence of tumor thrombus, and degree of tumor-vessel contact.

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

Assessment of resectability of extrahepatic bile duct cancer involves evaluating whether major vessels such as the hepatic artery, portal vein, and their main branches (vessels included in the surgical extent depending on the tumor's location and axial range) are invaded by the tumor and whether there are anatomical variations in hepatic vessels. To evaluate vascular invasion in preoperative CT or MRI images of patients with extrahepatic bile duct cancer, authors or we have reviewed one meta-analysis [119] and 15 retrospective studies [120]. Included original studies were all retrospective in nature. They were predominantly focused on criteria for evaluating vascular invasion or comparing the performance based on those criteria. Most of these studies reported the overall performance of imaging examinations in assessing the resectability of extrahepatic bile duct cancer. However, these studies had some limitations, including a small number of included patients and variations in patient characteristics (e.g., tumor location, type of imaging examination, reference standards such as pathology and surgical findings). Nevertheless, many studies adopted common criteria for assessing resectability, with Li and Lu's proposed method being one of the most widely used [120-128].

In imaging examinations, vascular invasion is indicated in the following cases: 1) If a blood vessel is occluded by the tumor, it suggests vascular invasion; 2) If a tumor thrombus is present in the blood vessel, it suggests vascular invasion; 3) If the tumor completely surrounds the blood vessel, it suggests vascular invasion [128].

When the tumor partially surrounds the blood vessel, the degree of tumor-vessel contact is evaluated [98,129]. Depending on the degree of loss of fatty interface between soft tissue shadow suspected to be a tumor and blood vessel, there is no contact (if the tumor-vessel fatty interface is maintained), abutment (if less than 50% of the vessel circumference is in contact with the tumor), or encasement (when more than 50% of the blood vessel circumference is in contact with the tumor). In cases where there is an abutment and a deformed blood vessel shape or encasement, there is a high possibility that blood vessels have been invaded. R0 (negative resection margins) resection is expected to be difficult without combined blood vessel resection. In cases where there is only an abutment without change in the shape of the blood vessel, the possibility of vascular invasion is uncertain. It is considered a condition in which R0 may be achieved after resection.

KQ9. In patients suspected of having extrahepatic bile duct cancer, the presence or absence of lymph node metastasis can be evaluated by size, shape, degree of contrast enhancement, and SUV on contrast-enhanced CT, MRI, or PET-CT.

Recommendation grade	A. Strong recommendation
Level of evidence	III. Low

A meta-analysis [130] evaluating the diagnostic capability of contrast-enhanced CT for lymph node metastasis in patients suspected of having extrahepatic bile duct cancer included five studies involving 136 patients. In that analysis, the sensitivity was 61% (95% CI: 28%–86%), while the specificity was 88% (95% CI: 74%–95%), indicating a relatively low sensitivity. Two retrospective studies [131,132] reported sensitivities of 65% and 50% for hilar cholangiocarcinoma, with specificity values of 53.8% and 89.1%. For distal cholangiocarcinoma, sensitivity was 25% with a specificity of 85.7%. Subsequent retrospective studies assessing the diagnostic capability of contrast-enhanced MRI for lymph node metastasis reported sensitivities ranging from 23.5% to 84.2% and specificities ranging from 66% to 97.6%, with an accuracy of 66% to 79.7%. These studies suggested that MRI has limitations in evaluating lymph node metastasis. Comparative studies between CT and MRI were conducted in three retrospective studies [98,133,134] involving 21, 27, and 70 patients. These studies found that there were not statistically significant different to detect lymph node metastasis between CT and MRI.

One retrospective study and two meta-analyses have assessed the diagnostic capability of PET-CT. In the retrospective study [135] conducted in 2021 that included 69 patients, sensitivities, specificities, and accuracies for early (early phase) or delayed (delayed phase) PET-CT were 50%, 67.3%, and 71% or 62.5%, 73.3%, and 76.8%, respectively. In the two meta-analysis studies, Lamarca et al. [135] reported sensitivities and specificities of 88.4% (95% CI: 82.6%–92.8%) and 69.1% (95% CI: 63.8%–74.1%), respectively, while Hu et al. [136] reported sensitivities and specificities of 51.6% (95% CI: 43.6%–59.5%) and 91.4% (95% CI: 87.3%–94.5%), respectively.

In a prospective study by Kim and colleagues [137] comparing PET-CT and CT, PET-CT exhibited significantly higher diagnostic accuracy (75.9% vs. 60.9%, $p = 0.004$) and specificity (88.2% vs. 64.7%, $p < 0.001$) compared to CT. However, in a meta-analysis by Ruys et al. [98], CT had higher sensitivity and specificity than PET-CT (sensitivity 61% vs. 42%, specificity 88% vs. 80%, $p = 0.04$). These differences were not statistically significant due to the inclusion of only one study in the PET-CT analysis. In a retrospective study [138] involving 36 patients, PET-CT had higher sensitivity, specificity, and positive predictive value than CT. This suggests that PET-CT is useful for evaluating lymph node metastasis, although it has limitations compared to CT.

In a meta-analysis [139] comparing PET-CT (11 studies) and MRI (5 studies), PET-CT exhibited significantly higher specificity than MRI (92% vs. 69%, $p = 0.04$), although its sensitivity was not significantly different from that of MRI (52% vs. 64%,

$p = 0.08$).

For evaluating lymph node metastasis in contrast-enhanced CT or MRI, criteria considered were: lymph nodes with a short axis size of 1 cm or larger, central necrosis, abnormal round morphology, heterogeneous enhancement, and lymph nodes showing more significant enhancement in the portal venous phase compared to the surrounding liver parenchyma. Some studies have suggested that combining size, round morphology, and heterogeneous enhancement criteria can provide higher positive predictive value than using size alone [140].

PET-CT studies have been conducted using criteria that include standardized uptake value (SUV) higher than the surrounding normal tissue or an SUV maximum (SUVmax) of 2.0–2.5 or greater as the threshold. However, these studies have demonstrated limited diagnostic accuracy of PET-CT for evaluating lymph node metastasis in imaging examinations. Generalizing these observations has limitations. Considering the possibility of lymph node metastasis is more appropriate when the mentioned criteria are present.

KQ10. Patients with suspected distant liver metastasis after CT imaging in extrahepatic cholangiocarcinoma can undergo additional liver MRI.

Recommendation grade	A. Strong recommendation
Level of evidence	III. Low

In studies analyzing the diagnostic ability of CT for distant metastasis in extrahepatic cholangiocarcinoma patients, CT exhibited a minimum sensitivity [131,141,142] as low as 50.0%. Factors contributing to reduced diagnostic accuracy included liver metastases smaller than 1 cm, peritoneal metastases, and N2 lymph node metastases.

A meta-analysis [143] regarding the diagnostic ability of resectability in extrahepatic cholangiocarcinoma has included 11 CT studies and 5 MRI studies. The pooled sensitivity was 95% (95% CI: 91%–97%) for CT and and 94% (95% CI: 90%–97%) for MRI, while the specificity was 69% (95% CI: 63%–75%) for CT and 71% (95% CI: 60%–81%) for MRI. There was no statistically significant difference ($p > 0.05$) between them. However, the assessment of resectability is influenced not only by distant metastasis, but also by factors such as the extent of longitudinal invasion in extrahepatic cholangiocarcinoma, lymph node metastasis, and vascular invasion. Therefore, the diagnostic ability of CT and MRI for diagnosing distant metastasis may differ.

Another noteworthy study [135] has focused on distinguishing between liver abscesses and metastasis using MRI in the context of periampullary cancer. Diagnositic indicatiors suggesting biliary abscess over liver metastasis encompassed size discrepancies between T1-weighted images and ampulla and arterial rim enhancements persisting until the portal venous phase. Incorporating these indicators, the accuracy can be increased to 90.0% (95% CI: 85.2%–94.9%). Nonetheless, that study included only 21 extrahepatic cholangiocarcinoma patients out of a total 72 patients. Moreover, the absence of external validation in that study underscores the need for further research.

KQ11. Treatment response of extrahepatic cholangiocarcinoma patients is evaluated by considering patient's clinical presentation, tumor markers, and imaging examinations collectively.

Recommendation grade	A. Strong recommendation
Level of evidence	III. Low

Currently, there are no standardized imaging guidelines established for postchemotherapy or postsurgery surveillance in extrahepatic cholangiocarcinoma patients. Nevertheless, a multitude of clinical trials investigating novel drug therapies have predominantly adopted the Response Evaluation Criteria in Solid Tumours (RECIST) as the benchmark criteria, with CT imaging being the modality of choice for assessing tumor response. Some studies have also utilized a combination of CT and MRI [113,144-150]. In 2019, the Consensus Recommendations by the Korean Society of Abdominal Radiology proposed that imaging examinations, including CT and MRCP, could be recommended for evaluating treatment response in extrahepatic cholangiocarcinoma patients. These recommendations also suggest using RECIST criteria for assessment [151].

Postsurgical recurrent cholangiocarcinoma typically manifests in the form of local recurrence, liver metastasis, lymph node metastasis, and peritoneal seeding [152]. In the realm of follow-up imaging, drawing a clear distinction between local recurrent cancer or malignant biliary stricture versus benign biliary stricture or granulation tissue is paramount. However, the lack of standardized radiological guidelines for differentiation remains a significant challenge, with research in this area being relatively sparse. Based on empirical evidence, potential indicators suggestive of local recurrent cancer include a pattern of increasing suspicious lesions on successive imaging, invasion of adjacent vessels and organs, moderate to severe enhancement, and progressive biliary stricture with localized wall thickening. In cases where local recurrent cancer is suspected during follow-up imaging, both short-term follow-up CT or MRI and PET-CT are frequently employed. According to European Society for Medical Oncology (ESMO) guidelines, after curative resection, surveillance examinations are recommended every 3 months for the first 2 years, every 6 months from year 2 to year 5, and then annually after 5 years [138]. NCCN guidelines recommend surveillance examinations every 6 months for the first 2 years after curative resection and then every 12 months until 5 years [153].

KQ12. For more accurate staging in patients with extrahepatic cholangiocarcinoma, FDG-PET imaging can be conducted.

Recommendation grade	A. Strong recommendation
Level of evidence	III. Low

There were a total of seven papers that examined the role of FDG-PET in patients diagnosed with extrahepatic cholangiocarcinoma. Most of these original studies focusing on FDG-PET had small sample sizes fewer than 100 participants.

According to a meta-analysis conducted by Huang, which drew upon on four studies, FDG-PET demonstrated a high sensitivity of 90% (95% CI: 77%–98%) and a moderate specificity of 79% (95% CI: 65%–94%) in diagnosing primary extrahepatic cholangiocarcinoma [137]. These results were comparable to those of MRI, which exhibited a sensitivity of 88% (95% CI: 81%–92%) and a specificity of 85% (95% CI: 74%–92%) [138].

Regarding staging with PET/CT, four research papers were found. Kim et al. [153] reported on the staging diagnostic performance in a retrospective study of 234 extrahepatic cholangiocarcinoma patients. Kim et al. [137] conducted a prospective study with 73 patients, Petrowsky et al. [154] conducted a prospective study with 33 patients and Kato et al. [155] conducted a prospective study with 30 patients. When the findings of these studies were combined, PET/CT exhibited a low sensitivity of 38% (54/143, range: 12%–44%), a high specificity of 94% (237/253, range: 95%–100%), and a moderate accuracy of 73% (291/396, range: 64%–80%) in diagnosing lymph node metastasis. In the case of diagnosing distant metastasis, PET/CT showed a high sensitivity of 82% (36/44, range: 58%–100%), a high specificity of 96% (330/345, range: 93%–100%), and a high accuracy of 94% (366/389, range: 88%–100%). In comparison, contrast-enhanced CT exhibited a moderate sensitivity of 63% (90/143, range: 24%–75%), a moderate specificity of 67% (94/140, range: 57%–86%), and a moderate accuracy of 73% (289/396, range: 57%–94%) in diagnosing lymph node metastasis. For the diagnosis of distant metastasis, contrast-enhanced CT showed a low sensitivity of 45% (20/44, range: 0%–92%), a high specificity of 83% (114/137, range: 63%–100%), and a high accuracy of 88% (265/302, range: 78%–94%). In summary, when compared to contrast-enhanced CT, PET/CT demonstrated lower sensitivity, higher specificity, and similar accuracy in diagnosing lymph node metastasis. However, PET/CT showed higher values in all aspects for diagnosing distant metastasis. Two papers also discussed the impact of PET/CT on treatment planning. Albazaz et al. [156] reported a treatment plan change rate of 24% (15/63, range: 20%–32%) based on PET/CT in a retrospective study of 22 extrahepatic cholangiocarcinoma patients, while Corvera et al. reported a similar rate in a prospective study [157] of 41 patients who underwent PET/CT in addition to contrast-enhanced CT or MRI.

Surgical treatment

KQ13. In cases where ductal dilation and a congenital pancreaticobiliary maljunction are not detected, prophylactic cholecystectomy can be performed (Grade A).

Recommendation grade	A. Strong recommend
Level of evidence	III. Low

There were a total of nine studies on surgical treatment of congenital pancreaticobiliary maljunction without ductal dilation. All nine these studies were retrospective patient-control group studies [90,158-165]. Among these studies, multicenter studies were exclusively conducted in Japan [90,160].

The first multicenter study in Japan was published in 2003. It reported a much higher incidence of gallbladder cancer compared to bile duct cancer in patients with congenital pancreaticobiliary maljunction without ductal dilation (93% vs. 6%) [160]. Based on that study, subsequent surgical treatment for patients with congenital pancreaticobiliary maljunction without ductal dilation was generally recommended to include prophylactic cholecystectomy. However, the second multicenter study as a follow-up study from Japan published in 2013 reported that approximately 42% of patients with congenital pancreaticobiliary maljunction without ductal dilation were found to have biliary tract cancer. In congenital pancreaticobiliary maljunction without ductal dilation group, gallbladder cancer accounted for 88.1%, while bile duct cancer accounted for 7.3%, indicating an increased incidence of bile duct cancer [90]. As a result, there is an argument that both gallbladder resection and prophylactic bile duct resection should be performed. However, the current consensus is that when gallbladder duct is not involved, gallbladder resection alone is generally considered sufficient due to varying reports on the incidence of bile duct cancer.

KQ14. Use of CT for residual liver volume measurement and liver function evaluation tests can predict function of the remaining liver after surgery.

Recommendation grade	A. Strong recommendation
Level of evidence	III. Low

Liver function after surgery depends on both the volume and function of the liver. One method that can assess liver volume is CT volumetry, which utilizes CT scans to measure the size of the liver. It is generally considered safe to perform liver resection when the FLR is greater than 25%–30% in patients with normal liver tissues. When patients have fatty liver, liver fibrosis, chronic cholangitis, or have undergone anticancer treatment, FLR of greater than 40% is considered safe. However, a limitation of CT volumetry is that it does not take into account individual patient characteristics. In cases where jaundice is present, such as in extrahepatic bile duct cancer, liver volume may not accurately reflect liver function, leading to potential measurement errors [166].

Ribero et al. [90] have identified preoperative cholangitis and

FLR < 30% as factors contributing to postoperative liver failure. Olthof et al. [167] have incorporated the presence of jaundice at diagnosis, preoperative cholangitis, and a total bilirubin level of > 2.9 mg/dL just before surgery into their predictive model for postoperative liver failure. Furthermore, they suggested considering surgery for elderly patients (≥ 69 years) with reduced liver regeneration capacity when the FLR was at least 45% [168].

Liver function evaluation typically includes common biochemical tests such as bilirubin, albumin, transaminases, prothrombin time, and platelet count. Clinical indicators such as the Child-Pugh classification can also be used However, they have limitations in predicting postoperative outcomes. Quantitative liver function evaluation tests such as the Indocyanine green (ICG) clearance test or 99mTc-mebrofenin hepatobiliary scintigraphy (HBS) are considered more effective in predicting postoperative liver failure [166,169].

The ICG clearance test is an indirect method for assessing overall liver function. It is recommended to perform this test when the total bilirubin level is below 2.0 mg/dL, as it may be less accurate in patients with jaundice [170].

In a study conducted by Kuboki et al. [169] involving 284 patients who underwent major liver and bile duct resection, an ICG-R15 value of 11.8% or higher was associated with an increased risk of severe complications, including postoperative liver failure. Yokoyama et al. [168] have reported that when the ICG clearance rate (ICGK) multiplied by the FLR is less than 0.05, there is a significant increase in postoperative mortality.

Liver function can be evaluated using HBS based on mebrofenin's uptake rate (MUR, %/min). An MUR greater than 2.7%/min indicates that a large liver resection can be safely performed. However, in the case of extrahepatic bile duct cancer, an MUR greater than 8.5%/min is recommended [169,171]. HBS testing is not suitable for patients with jaundice (total bilirubin > 2.9 mg/dL). Cholangiography should be performed before conducting the examination in these patients [169].

Given that extrahepatic bile duct cancer often involves liver damage, accurately predicting postoperative liver function and preventing liver failure requires a comprehensive analysis that incorporates not only liver volume, but also an additional assessment of liver function.

KQ15. What are indications for preoperative portal vein embolization (PVE) in patients with hepatobiliary cancer at the Department of Liver and Bile Duct Surgery?

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

In patients with normal liver function, if the postoperative remnant liver volume is expected to be less than 30%–40% or if postoperative remnant liver volume is predicted to be less than 40%–50% in cases of liver cirrhosis, cholestatic liver disease, and other conditions, preoperative PVE may be considered to reduce postoperative complications and mortality (Grade B).

In surgical contexts, if the post-surgical remaining remnant liver volume is determined to be insufficient, PVE presents as a viable intervention. There are no prospective studies delineating the exact threshold of remnant liver volume that necessitates PVE. Nevertheless, insights from several retrospective studies suggest a framework. Specifically, in the context of a normal liver, the remnant liver volume threshold for considering PVE stands at less than 30%–40%. For livers compromised by cirrhosis or cholestasis, the threshold elevates to be less than 40%–50% [172,173]. In addition to individual liver parenchymal conditions, consideration of liver function (ICG test values) can allow for a slightly higher range of predicted remnant liver volume when ICG levels are high [174].

There have been five comparative cohort studies (one prospective and four retrospective) on the efficacy and safety of PVE in patients with low predicted remnant liver volume [174-178]. An amalgamation of findings from the four retrospective studies illuminates that complications directly attributable to PVE are exceptionally rare. Furthermore, postsurgical complications and mortality rates did not show a discernible difference between patients who underwent PVE and those who did not. In some cases, outcomes for the PVE cohort appeared more favorable. Notably, the long-term survival after surgery remained unaffected by the employment of PVE [176-178].

Reinforcing this perspective, a large-scale international multi-institutional retrospective study using a case-control design enhanced by propensity score matching was undertaken. It unveiled that patients who underwent PVE experienced significantly fewer postoperative complications, notably a reduced rate of postoperative liver failure. Furthermore, they had a markedly lower postoperative mortality rate than those who did not opt for PVE [175].

KQ16. Is caudate resection necessary in hepatocellular carcinoma of the bile duct? For radical resection in hilar cholangiocarcinoma, consideration is given to caudate lobe resection (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

A total of 11 studies, including 9 retrospective cohort studies [91,179-186] and 2 meta-analyses [187,188], investigated results of caudate lobe resection in patients with hepatobiliary cancer at the Department of Liver and Bile Duct Surgery. The nine retrospective cohort studies revealed that when the caudate lobe was excised during hepatobiliary cancer surgery, there was a high rate of radical resection (76%–93.1%) [91,180,182,183,185]. Additionally, the 5-year survival rate was reported to be from 16% to 25% [91,179,181-183,186]. Notably, in four of these studies, complication rates following caudate lobe resection were

comparable to those in other groups without such resection [91,181,182,185].

In a meta-analysis of 8 studies by Birgin and colleagues [185], caudate lobe resection was found to significantly enhance overall survival (HR: 0.49, 95% CI: 0.32–0.75). The analysis also indicated that patients who did not undergo caudate lobe resection were more likely to have residual tumors during subsequent follow-ups (HR: 1.40, 95% CI: 0.77–1.13).

A separate meta-analysis by Yang et al. [186], which encompassed 10 studies, reported similar findings. Caudate lobe resection led to a substantially higher rate of radical resection (OR: 3.88, 95% CI: 2.18–6.90) and better long-term survival (HR: 0.45, 95% CI: 0.38–0.55) (Table 3) [91,177-184]. Furthermore, postoperative complications were not significantly increased in the group that underwent caudate lobe resection compared to the group in which the caudate lobe was preserved (OR: 0.93, 95% CI: 0.65–1.33).

KQ17. Appropriate lymph node dissection range in resection surgery for bile duct cancer

Recommendation grade	Expert consensus
Level of evidence	III. Low

In resection surgery for potentially resectable extrahepatic bile duct cancer, the removal of regional lymph nodes (hepatoduodenal ligament nodes - No. 8, peripancreatic nodes - No. 12, and posterior pancreatic nodes - No. 13) is recommended. Optionally, extended lymph node dissection (caval nodes - No. 9, superior mesenteric artery nodes - No. 14, and para-aortic nodes - No. 16) is advised (expert consensus).

We analyzed a total of two studies that reported the range of lymph node dissection in bile duct cancer patients. The study types included 3 retrospective studies and 1 patient-control group study. All these studies were focused on hilar cholangiocarcinoma. However, due to variations in patient selection criteria and treatment methods, it was challenging to analyze surgical outcomes based on the extent of lymph node dissection.

In retrospective studies, patients with superior mesenteric artery lymph node metastasis had a lower survival rate than those with only regional lymph node metastasis (5-year survival rate: 12.3% vs. 14.7%, $p = 0.004$) [189]. However, in multivariate analysis, the presence of superior mesenteric artery lymph node metastasis was not a significant prognostic factor [129]. The survival rate was similar between patients who underwent extended lymphadenectomy (No. 8, 9, 12, 13a, 14v, 16) and those who underwent regional lymphadenectomy (No. 8, 12, 13a) when superior mesenteric artery lymph node dissection was performed (5-year survival rate: 12% vs. 31%, $p = 0.135$). In the patient-control group study, patients who underwent extended lymph node dissection (No. 8, 9, 12, 13a, 14v, 16) had a

Table 3. Survivla according to caudate lobectomy

Author	Year	Comparison group (caudate lobe resection)	n	Complication rate (%)	*p*-value	R0 resection rate (%)	*p*-value	Survival rate, % (5 yr)	*p*-value
Gazzaniga et al. [177]	2000	Yes	17	N/A	-	N/A	-	25.0	N/A
		No	29					0	
Cho et al. [178]	2012	Yes	62	N/A	-	81.6	0.01	N/A	-
		No	34			60.0			
Kow et al. [179]	2012	Yes	70	4.3	0.301	91.4	0.210	66.0	< 0.011
		No	57	8.8		84.2		30.0	
Wahab et al. [180]	2012	Yes	80		NS	71.2	< 0.001	28.0	< 0.001
		No	79			38.0		5.0	
Cheng et al. [181]	2012	Yes	137	27.7	0.39	89.1	< 0.01	16.0	< 0.01
		No	34	20.6		35.3		6.0	
Song et al. [91]	2013	Yes	101	N/A	-	93.1	0.003		0.003
		No	76			77.6			
Abd ElWahab et al. [182]	2016	Yes							
		No							
Bhutiani et al. [183]	2018	Yes	90	59	NS	76.0	0.01	5.6	NS
		No	166	66		60.0		10.2	
Geers et al. [184]	2020	Yes	56					DFS	0.048
		No	32						

N/A, not available; NS, not significant; DFS, disease free survival.

higher survival rate than those who underwent regional lymph node dissection (No. 8, 12, 13a) (after R0 resection, median overall survival: 33 months vs. 21 months, $p = 0.044$). However, after propensity score matching, the survival rate improvement in the extended lymph node dissection group was not observed. There was no significant difference in postoperative complication rate between the two groups.

KQ18. In patients with suspected vascular invasion of the portal vein or hepatic artery in bile duct cancer, should vascular resection be performed?

In cases where portal vein invasion is suspected, portal vein resection (PVR) can be considered (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

In cases where hepatic artery invasion is suspected, arterial resection may be considered in selected patients (Grade D).

Recommendation grade	D. Inconclusive
Level of evidence	III. Low

To investigate the utility of liver resection, including resection of major blood vessels (portal vein and hepatic artery) in the surgical treatment of hepatobiliary cancer, one meta-analysis and 16 retrospective cohort study data were referenced. However, prospective randomized controlled trials were not reported.

Portal vein resection

In a retrospective cohort study comparing a group that underwent PVR(+) and a group that did not PVR(–) during surgery for extrahepatic bile duct cancer, the following observations were made:

(1) Postoperative mortality was higher in the PVR group (range: 0%–19%) than in the group without PVR (range: 0%–16%) [190-198]. However, some studies reported lower mortality rates in the PVR group [199,200]. A meta-analysis involving 1,996 patients, which combined results of these studies, indicated that the average mortality rate was 6.2% in the PVR group and 4.0% in the group without PVR, with the PVR group showing a tendency of increased mortality (OR: 1.61, 95% CI: 1.02–2.54, $p = 0.04$) [201].

(2) The occurrence of postoperative complications increased in some studies in the PVR group [196,199]. However, most studies showed no significant difference in complication rate between the two groups [190-195,197,198,200]. A meta-analysis involving 2,189 patients did not demonstrate an increase in complications due to PVR either (OR: 1.03, 95% CI: 0.74–1.42, $p = 0.88$). However, as mentioned earlier, PVR was associated with a higher incidence of liver failure (OR: 1.60, 95% CI: 1.19–2.16, $p = 0.002$) [201].

(3) A total of 18 retrospective cohort studies compared survival rates and a meta-analysis of these studies revealed that 3-year and 5-year survival rates were significantly lower in the group without PVR than in the group with PVR (3-year OS: OR = 0.45, 95% CI: 0.36–0.57, $p < 0.00001$; 5-year OS: OR = 0.52, 95% CI: 0.35–0.76, $p = 0.0008$) [201].

However, according to a study by Lurje and others [199], the PVR group often had more advanced tumors (higher T-stage) and a higher incidence of lymph node metastasis (higher N-stage), both of which are adverse prognostic factors for extrahepatic bile duct cancer. This suggests that the lower 3-year and 5-year survival rates in the PVR group might be attributed not to adverse effects of PVR itself, but to the fact that surgery was performed at a more advanced stage. On the other hand, cases where portal vein invasion was suspected but PVR was not performed ultimately resulted in R1 or R2 resections. Therefore, comparing survival rates of the PVR group with those of the group without PVR might be more valid when considering R1 or R2 resection patients. Some studies have shown that PVR resulted in a significant improvement in survival when compared to R1 or R2 resection patients [200,202,203].

In summary, among surgical procedures for extrahepatic bile duct cancer, PVR may potentially lead to an increased postoperative mortality rate. However, complications do not appear to show significant increases. In cases where PVR is not performed, resulting in incomplete resection, it is reasonable to expect an improvement in survival compared to cases with non-resection. Therefore, it is advisable to recommend the implementation of PVR.

Hepatic artery resection

Studies on hepatic artery resection (HAR) during surgery for extrahepatic bile duct cancer are limited to relatively small cohorts of retrospective cohort studies. When comparing a group that underwent HAR(+) with a group that did not HAR(–) during surgery for extrahepatic bile duct cancer, the following observations were made:

(1) Postoperative mortality rates were significantly higher in the HAR group in all five studies [190-192,196,198]. A meta-analysis of 1,206 patients confirmed a significantly higher mortality rate in the HAR group (OR: 4.20, 95% CI: 1.88–9.39, $p = 0.0005$).

(2) The incidence of surgical complications was higher in the HAR group in three retrospective studies [192,198,204]. However, two studies [196,205] reported that HAR did not increase the occurrence of complications. A meta-analysis involving 626 patients found no significant difference in the occurrence of complications between these two groups (OR: 1.03, 95% CI: 0.74–1.42, $p = 0.88$) [201]. However, when specifically examining hepatic insufficiency, complications were more frequently observed in the HAR group (OR: 1.77, 95% CI: 1.23–2.54, $p = 0.002$) [201].

(3) Survival rate analysis showed that 3-year/5-year survival rates were 54.12%/46.75% in the group without HAR and 43.90%/27.81% in the HAR group, with the HAR group showing significantly lower survival rates (3-year OS: OR = 0.55, 95% CI = 0.41–0.74, $p < 0.0001$; 5-year OS: OR = 0.43, 95% CI = 0.32–0.57, $p < 0.00001$) [201]. However, histological examination of the resected tissue showed that the HAR group had a R0 resection success rate similar to the group without HAR (OR: 0.77, 95% CI: 0.37–1.61, $p = 0.49$), suggesting that HAR could effectively remove arterial invasion [201]. Ultimately, lower survival rates in the HAR group were more likely due to the fact that HAR was performed on patients with more advanced disease rather than direct effects of HAR.

HAR does not appear to significantly increase the incidence of surgical complications, although it can lead to a marked increase in postoperative mortality. Thus, the safety of the procedure is compromised. However, there is insufficient evidence to assess its effect in improving survival rates. Therefore, HAR in cases of suspected hepatic artery invasion in extrahepatic bile duct cancer should be considered for selected patients based on individual considerations, taking into account the patient's overall cancer stage and physical condition.

KQ19. During surgery, in the frozen section examination, is additional resection necessary for carcinoma in situ/high-grade dysplasia (CIS/HGD)?

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

During surgery, in the frozen section examination of the resected specimen, it is not recommended to expand the surgical scope for additional resection when CIS/HGD is identified to secure negative margins (Grade B).

A total of 13 retrospective studies compared survival and recurrence rates between patients who underwent R0 resection and those with CIS/HGD or R1 resection [205-217]. Notably, randomized controlled studies assessing patients diagnosed with CIS/HGD via frozen section examinations during surgery and whether they were given further resection could not be found. Those retrospective studies primarily compared final histological results, including R0 resection, R1cis, and R1 resection, with the ultimate goal of achieving R0 resection during surgery.

Within these retrospective studies, survival rates generally did not vary significantly between patients achieving R0 resection and those where CIS/HGD was detected in the resected specimen. However, the R1 resection group (indicating a positive invasive carcinoma) recorded a significantly decreased survival rate (Table 4). Five-year survival rates spanned from 32% to 78.7% for the R0 resection group, 22.2% to 69% for the R1cis resection group, and 12% to 34.9% for the R1 resection group (Table 4). In instances of early-stage bile duct cancer, particularly without lymph node metastasis or at stages T2 or below, the R0 resection group exhibited markedly higher survival rates than the R1cis resection group [218,219].

For patients without lymph node metastasis, the R0 resection group demonstrated considerably better survival outcomes than the R1cis resection group. Nevertheless, their survival rates did not show significant disparities in cases with lymph node metastasis. In cases without lymph node metastasis, there was a significant improvement in survival rate when securing negative margins through additional resection in the R1cis group [218]. A Nagoya University study encompassing early-stage Tis-T2N0M0 bile duct cancer patients noted that those with CIS/HGD in their resected specimen had lower survival rates than the R0 resection group. These findings suggest that more efforts are needed to achieve a radical resection with negative margins, especially for CIS/HGD in early-stage bile duct cancers. Contrarily, another study comparing T1, T2 patient groups and the entire patient population did not report any difference in survival or recurrence rate between CIS/HGD and R0 groups [220].

When evaluating a patient with presumed early-stage bile duct cancer, the patient's overall condition and surgical scope must be integrated. Hence, aggressive surgery may be essential for enhancing survival rates via R0 resection, especially if the surgical scope is expanded. However, the final determination of early-stage extrahepatic bile duct cancer can only be ascertained through postsurgical histological examination, which poses certain intraoperative limitations.

R0 resection is clinically the most effective treatment. In cases where CIS/HGD is detected, additional resection may require an excessive expansion of the surgical scope. Additional resection may not always be feasible, particularly when securing the proximal resection margin during major liver resection or segmental resections of hilar cholangiocarcinoma. In cases of hilar cholangiocarcinoma, there may be situations where a major liver resection is necessary to secure the proximal resection margin during hepaticoduodenectomy (HPD). This procedure is associated with high postoperative complications and mortality rates of 2.4%–29.4%. Furthermore, most studies have comparatively long follow-up periods with a relatively small number of patients, typically 15 to 40 patients, indicating that HPD is not a frequent procedure [206-208,221,222].

In conclusion, while malignancy and recurrence are possible in CIS/HGD cases, retrospective studies did not highlight a significant difference in survival or recurrence between R0 and other groups (Table 4). Thus, if a maximal bile duct margin is achieved, further resection is not typically advocated. Limitations of studies included in this analysis include their retrospective nature, the small number of patients with HGD and CIS in each study, and the inability to exclude effects of postoperative radiotherapy and other treatments. It is important to consider that in all studies, maximum efforts were made to achieve R0 resection, which might have included additional

Table 4. Literatures

Study	Study period	Total no	Cancer	R0	CIS/HGD	R1	R0 5YSR (MST)	Rcis 5YSR (MST)	R1 5YSR (MST)	Survival rate difference
Shin et al. [209], 2020	2001–2015	306	PHCC	217 (71.0%)	18 (5.8%)	71 (23.2%)	34.5% (36 mon)	44.4% (41 mon)	21.0% (25 mon)	R0 = R1cis > R1
Yasukawa et al. [205], 2021	1990–2019	121	diBD	92 (76.0%)	15 (12.4%)	14 (11.6%)	49.5%	32.7%	19.7%	LN(–); R0 > R1cis = R1 LN(–); R0 = R1cis R1cis = R1 R0 > R1 LN(+)
Park et al. [206], 2019	2008–2016	193	diBD	174 (90.2%)	12 (6.2%)	7 (3.6%)	59.3%	59.5%	14.3%	R0 = R1cis > R1
Yoo et al. [207], 2018	2001–2012	96	PHCC	59 (61.4%)	6 (6.3%)	31 (32.3%)	33 mon	30 mon	21 mon	R0 = R1cis R1cis vs. R1 $p = 0.050$
Lee et al. [208], 2012	2000–2009	162	PHCC	119 (73.5%)	6 (3.7%)	37 (22.8%)	R0 44.5%		R1 34.9%	R0 = R1
Nakanishi et al. [210], 2010	1989–2007	125	EHBD	96 (76.8%)	10 (8.0%)	19 (15.2%)	32.0% (38 mon)	48.0% (51 mon)	- (17 mon)	R0 = R1cis > R1
Sasaki et al. [211], 2007	1985–2005	128	EHBD	105 (82.0%)	12 (9.4%)	11 (8.6%)	35.5% (992 day)	22.2% (1,097 day)	- (373 day)	R0 = R1cis > R1
Wakai et al. [212], 2005	1988–2002	84	EHBD	64 (76.2%)	11 (13.1%)	9 (10.7%)	46.0%	69.0%	-	R0 = R1cis > R1
Tsukahara et al. [213], 2017	1998–2013	172	EHBD (-Tis-2N0M0)	148 (86.0%)	18 (10.5%)	6 (3.5%)	78.7%	35.1% (4.4 yr)	- (1.1 yr)	R0 > R1cis > R1
Han et al. [214], 2014	1995–2007	464	EHBD	340 (73.3%)	39 (8.4%)	85 (18.3%)	44.5% (41 mon)	20.7% (29 mon)	12.0% (18 mon)	R0 > R1cis > R1
Higuchi et al. [215], 2010	1972–2006	256	EHBD	185 (72.3%)	13 (5.1%)	17 (6.6%) R241 (16.0%)	54.7%	52.4%	17.6%	R0 = R1cis R1cis > R1
Kurahara et al. [216], 2017	2002–2014	100	EHBD	69 (69.0%)	16 (16.0%)	15 (15.0%)				R0 = R1cis R1cis > R1
Higuchi et al. [217], 2017	2004–2013	163	PHCC	113 (69.3%)	22 (13.5%)	28 (17.2%)				R0 = R1cis R1cis = R1 R0 > R1

5YSR, 5-year survival rate; MST, median survival time; LN(–), lymph node negative patient group; LN(+), lymph node positive patient group; =, survival rate not different significantly; >, survival rate significantly different (R0 > R1; survival rate of R0 was significantly better than survival rate of R1); PHCC, perihilar cholangiocarcinoma; EHBD, extrahepatic bile duct cancer; diBD, distal bile duct cancer; CIS/HGD, carcinoma in situ/high-grade dysplasia.

resection or an expansion of the surgical scope, even in cases of CIS/HGD.

KQ20. Is minimally invasive surgery possible for extrahepatic cholangiocarcinoma?

Minimally invasive surgery can be performed for distal bile duct cancer (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	II. Moderate

A meta-analysis study [223] comparing minimal invasive pancreaticoduodenectomy and open surgery, which included two randomized controlled trials and 29 cohort studies with a total of 58,622 patients (49,875 in the open surgery group and 8,716 in the minimal invasive surgery group), found that the risk ratio for disease-free survival and overall survival at 3 years and 5 years favored minimal invasive surgery, although there was no statistically significant difference. Another meta-analysis study comparing the frequency of postoperative complications between the two groups found no significant difference, although the minimal invasive surgery group had less bleeding and a shorter hospital stay [223].

In a 2021 study, Kim evaluated the efficacy and outcomes of minimally invasive pancreaticoduodenectomy in comparison

with the traditional open surgical approach for treating proximal cholangiocarcinoma utilizing propensity score matching [224]. This investigation encompassed a cohort of 91 patients subjected to laparoscopic procedures and another 335 patients who underwent conventional open surgeries [224]. Results showed that the minimal invasive surgery group had less estimated intraoperative bleeding and shortened hospital stays. However, long-term outcomes including cancer recurrence were not significantly different. It was noteworthy that the time taken for the minimally invasive surgery group was observed to be longer, a finding consistent with other studies.

The feasibility of minimally invasive surgery for proximal cholangiocarcinoma has been affirmed. Nevertheless, certain parameters including invasion of major blood vessels such as the portal vein, the use of neoadjuvant chemotherapy or radiation therapy, obesity, and so on were excluded from comparative studies. Consequently, it is imperative to underscore that the applicability of this surgical modality may not be universal for all patients. Rigorous patient selection remains paramount [225-227]. Additionally, proficiency and experience of the surgeon play a pivotal role in the success of minimal invasive surgeries. While a universally accepted benchmark for this expertise remains elusive, prevailing literature advocates that institutions conducting in excess of 20 pancreaticoduodenectomies annually might be well-suited to adopt the minimally invasive approach [225,228].

Randomized controlled studies comparing minimal invasive surgery and open surgery for distal cholangiocarcinoma could not be found. Although retrospective comparative studies have been reported, there is currently insufficient evidence to make a recommendation. The grade of recommendation is pending [229]. Among the 9 studies included, 8 were conducted in China. In addition, the number of cases for minimally invasive surgery was less than 20 in all studies except for one study, indicating a small sample size. Furthermore, there was a lack of long-term follow-up data necessary for comparing oncological outcomes, including cancer recurrence and long-term observations [229-239]. Therefore, based on the discussions within the committee, it was determined that there was insufficient evidence to make a recommendation regarding the use of minimally invasive surgery for distal cholangiocarcinoma. Thus, a recommendation is pending.

KQ21. Tests required for postsurgery surveillance of extrahepatic cholangiocarcinoma (tumor markers and CT scans)

Imaging tests and tumor marker tests are conducted every 3–6 months for a minimum of 5 years (Grade A).

Recommendation grade	A. Strong recommendation
Level of evidence	IV. Very low

The optimal surveillance period and imaging modalities following surgical resection for extrahepatic cholangiocarcinoma have not been definitively established yet. Currently, there are no comparative studies, retrospective studies, or randomized controlled trials that provide conclusive data on the best frequency or choice of imaging methods.

The NCCN guidelines [240] suggest conducting imaging tests every 3–6 months for 2 years after surgery and then at intervals of 6–12 months for the subsequent 5 years. These tests should include CT scans and tumor marker assessments as baseline. Chest CT scans may also be performed. In cases where cancer recurrence or progression is confirmed or suspected, additional imaging studies such as MRI or PET scans are recommended. PET scans can be beneficial not only in staging before surgery, but also in postoperative surveillance for detecting occult metastatic disease and recurrent cancer [240,241]. Tumor marker tests (such as CEA and CA19-9) are useful in the diagnosis of cholangiocarcinoma. They can also be conducted during postsurgery surveillance.

The ESMO guidelines propose a slightly different approach. Postoperatively for extrahepatic cholangiocarcinoma, they recommend clinical evaluations every three months for the initial two years. These evaluations should encompass tumor marker assessments, blood tests, and both abdominal and chest CT scans. Following this period, regular follow-up evaluations can be performed at 6-month intervals and once a year for up to 5 years in some cases [242]. The interval might be influenced by the patient's initial staging. Typically, a 3–6-month frequency is embraced, with adjustments made according to individual patient's specific circumstances. Additionally, if recurrence is suspected but not clearly identified through imaging tests, the follow-up period may be reduced [242].

In cases where recurrence is suspected, confirmatory tests such as PET-^{18}FDG, MRI, MRCP, contrast-enhanced US, EUS, and tissue biopsies of the suspected areas can be performed to confirm the recurrence [135,152].

Pathology

KQ22. Pathological diagnostic report for frozen section examination of the resected bile duct during surgery for extrahepatic cholangiocarcinoma

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

The pathological diagnostic report for frozen section examination of the resected bile duct during surgery for extrahepatic cholangiocarcinoma includes the following details (Grade B):

- Negative (no tumor in this specimen)/Low-grade dysplasia (BilIN-1 or 2)
- Atypical cell present or indefinite for neoplastic lesion (clinical correlation is recommended)
- HGD (BilIN-3)

• Positive (invasive carcinoma)

KQ23. Gross examination method for surgical specimens of extrahepatic cholangiocarcinoma

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

Based on tumor's location, surgical specimen for extrahepatic cholangiocarcinoma may encompass the CBD alone or include the CBD, common hepatic duct, cystic duct, and gallbladder. The common hepatic duct is formed when left and right intrahepatic ducts emerging from the liver merge. When the cystic duct joins the common hepatic duct, it becomes the CBD. The CBD continues downward, passing through the pancreatic parenchyma and joins with the pancreatic duct to open into the duodenum at the ampulla of Vater. The extrahepatic bile duct is surrounded by connective tissues, while the upper portion of the CBD is encased within the pancreatic parenchyma. Therefore, surgical specimen for extrahepatic cholangiocarcinoma can extend from below the portal vein down to the upper border of the pancreatic parenchyma.

Surgical resection margins encompass proximal and distal margins of the bile duct as well as circumferential margins where the duct is separated from surrounding connective tissues (radial/circumferential margin).

During gross examination of the surgical specimen, the pathologist confirms the presence of proximal or distal margins of the bile duct and makes an incision along the axis of the duct to check for any visible abnormalities within the duct. In cases where the gallbladder and cystic duct is included, the direction can be determined by ensuring that the cystic duct points downward. However, if only a portion of the CBD is resected, it can be challenging to identify proximal and distal margins. In such instances, markings placed during surgery or other indicators in the operating room are used as references. The tumor's location is confirmed. Its size and margin of resection are then measured. The tumor's size is recorded in a format like 2.0 × 2.0 cm and the margin distance is described in centimeters. Lymph nodes are examined visually in connective tissues around the CBD and cystic duct to obtain as many as possible. After fixation in formalin for 24 hours, serial longitudinal sections are made along the axis of the CBD at regular intervals, including both proximal and distal resection margins. These sections ensure that all continuous cross-sections of the tumor are included. While longitudinal sections along the axis of the duct are given priority, cross-sectional sections perpendicular to the duct's axis are also possible. Regardless of the direction, all continuous cross-sections of the tumor must be included, with an emphasis on including the adjacent normal epithelium whenever possible. This meticulous examination provides crucial information for diagnosing and staging cholangiocarcinoma, guiding treatment decisions and postoperative follow-up.

KQ24. Essential contents to include in the pathological diagnosis of extrahepatic cholangiocarcinoma surgical specimens

Recommendation grade	A. Strong recommendation
Level of evidence	I. High

Staging of extrahepatic bile duct cancer (recommendation)

Staging of extrahepatic cholangiocarcinoma (distal cholangiocarcinoma) is reported according to the TNM classification of the 8th edition of the AJCC [243]. The T classification is determined based on the depth of tumor invasion. The N classification is based on the number of lymph node metastases and the M classification is determined by the presence of distant metastasis.

Assessment of tumor invasion depth (T stage)

Staging of the tumor is defined as follows. The pT stage (T stage) is determined based on the depth of tumor invasion. The depth of tumor invasion is measured in centimeters (cm) as the vertical distance from the basal membrane of adjacent normal epithelium, epithelial dysplasia, or ductal dysplasia to the deepest invading tumor cells [244]. In cases where the tumor causes significant distortion and makes it difficult to observe adjacent normal epithelium, epithelial dysplasia, or ductal dysplasia, the distance to the deepest invading tumor cells is measured based on the appearance of the surrounding ductal wall. The depth of invasion is most accurately measured on slides. In cases involving fibrosis, there might be a difference between the deepest representative section observed with naked eyes and the slide where the tumor's deepest invasion is evident. Therefore, it is important to create consecutive sections with the tumor entirely included and measure the tumor's size and depth accurately. Hence, it is crucial to measure the tumor invasion depth in all consecutive section slides of the tumor, with a focus on selecting the maximum value for inclusion in the T classification. In cases of tumors protruding into the ductal lumen, the maximum depth of invasion should be measured vertically from the basal membrane of adjacent normal epithelium, epithelial dysplasia, or ductal dysplasia.

- pTX: Primary tumor cannot be assessed
- pTis: CIS/HGD
- pT1: Tumor invades the bile duct wall with a depth less than 0.5 cm
- pT2: Tumor invades the bile duct wall with a depth of 0.5–1.2 cm
- pT3: Tumor invades the bile duct wall with a depth greater than 1.2 cm
- pT4: Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

Lymph node metastasis evaluation (N stage)

Lymph node involvement is determined based on the num-

ber of involved lymph nodes evaluated from the surrounding lymph nodes. Adequate effort should be made to ensure the maximum number of appropriate lymph nodes through thorough visual inspection of the periductal connective tissue. Although the recommended minimum number of lymph nodes for diagnosis of bile duct cancer has not been established, if typically fewer than 12 lymph nodes are examined in gastrointestinal tumors, there might be a risk of underestimating the N stage. In cases where the number of lymph nodes is insufficient, additional visual inspections may be necessary to find more lymph nodes.

- pNX: Regional lymph nodes cannot be assessed
- pN0: No regional lymph node metastasis
- pN1: Metastasis in one to three regional lymph nodes
- pN2: Metastasis in four or more regional lymph node

Assessment of metastasis (M stage)

Remote metastasis is described with the specific location of the metastasis if it is present. Remote metastasis should be confirmed based on clinical findings rather than just through pathological examination. Clinical history and imaging findings should be taken into account.

- pM0: No distant metastasis
- pM1: Distant metastasis

Staging of extrahepatic bile duct cancer (recommendation)

Staging of extrahepatic bile duct cancer (hilar cholangiocarcinoma) is reported according to the TNM staging system of the AJCC 8th edition [243]. T staging assesses the extent of tumor invasion. N staging looks at the number of lymph nodes involved. M staging is determined by the presence or absence of distant metastasis.

Assessment of extent of tumor involvement (T stage)

The stage of a tumor is defined as follows. The pT stage is determined based on the degree to which the tumor invades adjacent structures [244]. It is essential to determine if the tumor has invaded beyond the bile duct into the surrounding adipose tissue, liver parenchyma, or major vascular structures. To do this, creating continuous sections of the majority of the tumor for examination on slides is crucial for an accurate diagnosis.

- pTX: Primary tumor cannot be assessed
- pTis: CIS/HGD
- pT1: Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
- pT2: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
- pT2a: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
- pT2b: Tumor invades adjacent hepatic parenchyma
- pT3: Tumor invades unilateral branches of the portal vein or hepatic artery
- pT4: Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Lymph node metastasis evaluation (N stage)

Lymph node metastasis is evaluated by examining surrounding lymph nodes. It is defined as follows, with the number of metastatic lymph nodes determining the evaluation. It is important to secure an adequate number of lymph nodes through thorough visual inspection of the pericholedochal connective tissue. While there is no established minimum number of lymph nodes recommended for the diagnosis of bile duct cancer, it is possible that the N-stage evaluation could be underestimated when fewer than 12 lymph nodes are examined, as is commonly done for digestive system tumors. In cases where an insufficient number of lymph nodes are examined, additional visual inspections may be necessary to find more lymph nodes.

- pNX: Regional lymph nodes cannot be assessed
- pN0: No regional lymph node metastasis
- pN1: Metastasis in one to three regional lymph nodes
- pN2: Metastasis in four or more regional lymph node

Assess for metastasis (M stage)

The definition of distant metastasis is as follows. In cases where metastasis is present, the specific location of metastasis should be described. Distant metastasis is often identified through clinical observations and imaging findings rather than pathological confirmation. Thus, it is essential to refer to clinical history, imaging results, and other relevant information when determining its presence.

- pM0: No distant metastasis
- pM1: Distant metastasis

Histological type and grade

Histological types are reported according to the World Health Organization (WHO) classification of digestive system tumors [245].

Adenocarcinoma is the most common and representative histological type. Many other tumor types are derived from this type. Adenocarcinoma is further classified based on differentiation into well-differentiated, moderately differentiated, and poorly differentiated subtypes. Discrepancies in differentiation between preoperative biopsy tissues and surgical specimens can occur due to intratumoral heterogeneity of tumor differentiation.

Intraductal papillary neoplasm of the bile duct is characterized by formation of papillary-shaped lesions on the bile duct mucosa. It can be visually observed growing inside the duct. It may include invasive components in 40%–80% of cases, necessitating a thorough histopathological examination of the entire lesion.

Adenosquamous carcinoma often arises from adenocarcinoma. It can be diagnosed as adenosquamous carcinoma when more than 30% of the composition is observed as squamous cell carcinoma after a thorough histological examination of the proportion of adenocarcinoma and squamous cell carcinoma.

Mixed adenoneuroendocrine carcinoma is a rare cancer type in which both adenocarcinoma and neuroendocrine tumors are observed together. The diagnosis is made based on the proportion of the two tumors after a thorough histological examination. Classification of included neuroendocrine tumors follows the criteria for mitosis and Ki-67 labeling index as specified in the WHO classification of digestive system tumors.

- Adenocarcinoma
- Intraductal papillary neoplasm with an associated invasive carcinoma
- Mucinous cystic neoplasm with an associated invasive carcinoma
- Mucinous adenocarcinoma
- Clear cell adenocarcinoma
- Signet-ring cell carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Mixed adenoneuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Small cell neuroendocrine carcinoma
- Neuroendocrine carcinoma (poorly differentiated)

Histological grading is reported based on tumor differentiation as follows.

- Grade 1: Well differentiated (greater than 95% of tumor composed of glands)
- Grade 2: Moderately differentiated (50% to 95% of tumor composed of glands)
- Grade 3: Poorly differentiated (less than 50% of tumor composed of glands)
- Grade 4: Undifferentiated

Tumor location, size, resection margin assessment, and presence of epithelial lesions

Tumor location: during gross examination, the location of the tumor is assessed by opening the bile duct along its axis. The location of the tumor is reported in terms of whether it is in the CBD, hepatic ducts, cystic duct, gallbladder, periampullary region, or intrahepatic ducts (horizontal extension). The center of the tumor is also evaluated for its specific position. Additionally, the report should include whether the tumor has invaded surrounding structures such as adjacent connective tissues, pancreatic parenchyma, peri-ampullary region, duodenum, hepatic parenchyma, or major blood vessels (vertical extension).

Tumor size: tumor size is measured in centimeters (cm) by determining both the longest axis (longest length) and the perpendicular axis (shortest length). Measuring the size from continuous slide sections under a microscope provides a more accurate measurement than visual measurements with naked eye.

Resection margin assessment

Extrahepatic bile duct resection specimens: proximal biliary duct margin, distal biliary duct margin, and margin around the bile duct where the bile duct has been dissected from soft tissue are evaluated.

Pancreaticoduodenectomy specimen: distal biliary tract margin, pancreatic neck margin, pancreatic SMV/PV sulcus, retroperitoneal margin, proximal gastrointestinal tract margin, distal gastrointestinal tract margin, and margin around the bile duct are evaluated.

For hilar cholangiocarcinoma specimens, liver parenchymal resection margin, proximal bile duct resection margin, distal bile duct resection margin, and resection margin around the bile duct are evaluated.

For each resection margin, the presence or absence of tumor infiltration is reported. If the margin is negative, the safety distance between the tumor and the resection margin is measured. It is important to assess whether a sufficient safety distance has been achieved, as it has been suggested that a distance of less than 0.5 cm is associated with a higher risk of recurrence compared to distances of 0.5 cm or more [246]. Additionally, if there are high-grade epithelial lesions present at the resection margin, this information can be reported as an additional note.

Presence of intraepithelial lesions or mucosal dysplasia in adjacent epithelium

If there is concomitant intraepithelial lesions or mucosal dysplasia in adjacent epithelium, it may be reported as an additional pathological finding because the presence of such dysplasia increases the risk of recurrence. In such cases, lower-grade dysplasia might be observed in surgical specimens outside of the tumor region. This is not reported. The focus should primarily be on reporting HGD or BilIN 3 lesions.

Chemotherapy

KQ25. Postoperative adjuvant chemotherapy drugs in patients with radical resection for bile duct cancer

Postoperative adjuvant therapy with fluoropyrimidine-based chemotherapy is recommended for patients with radical resection of extrahepatic bile duct cancer (Grade A).

Recommendation grade	A. Strong recommendation
Level of evidence	I. High

Research on adjuvant therapy for patients with bile duct can-

cer has been ongoing for a long time. However, due to diverse clinical characteristics and surgical techniques associated with intrahepatic bile duct cancer, extrahepatic bile duct cancer, and gallbladder cancer, large-scale clinical studies have not been conducted yet. As a result, until recently, there was no standard treatment as postoperative adjuvant chemotherapy.

While retrospective studies and meta-analyses have shown that adjuvant chemotherapy/radiation therapy may improve survival in patients with positive surgical margins or lymph node involvement in bile duct cancer, it is challenging to establish a definitive standard regimen for adjuvant chemotherapy [247]. The European Study Group for Pancreatic Cancer (ESPAC)-3 periampullary trial was a prospective comparative phase III study that compared observation alone to treatment with 5-fluorouracil (5-FU)/leucovorin and gemcitabine in patients who underwent surgery for periampullary tumors. This multicenter study involved bile duct cancer patients of over 100 institutions from Europe, Australia, Japan, Canada, and other regions [248]. Although the number of bile duct cancer patients in the study was limited to only 96 out of 428 patients and the evidence for postoperative adjuvant chemotherapy in bile duct cancer was still insufficient, adjusted survival analysis showed that the group receiving adjuvant chemotherapy had better overall survival than the observation group (HR: 0.75, $p = 0.03$). Based on these findings, the 5-FU/leucovorin regimen has been used as a postoperative adjuvant therapy for patients with radically resected bile duct cancer in South Korea. Recently, three comparative studies on adjuvant therapy for bile duct cancer have been reported. The PRODIGE 12-ACCORD 18 study was a phase III study conducted in France, comparing surveillance with gemcitabine-oxaliplatin (GEMOX) combination therapy in a total of 196 patients with bile duct cancer. While this study showed a potential difference in relapse-free survival between the GEMOX group (30.4 months) and the surveillance group (18.5 months, $p = 0.48$), there was no statistically significant difference in overall survival (75.8 months for the GEMOX group and 50.8 months for the surveillance group, $p = 0.74$). The BCAT phase III study conducted in Japan focused on a total of 226 patients with perihilar and intrahepatic bile duct cancer. This study compared a group of patients receiving gemcitabine monotherapy with a group undergoing postoperative surveillance. Similar to the PRODIGE 12-ACCORD 18 study [249], the BCAT study did not show a significant difference in progression-free survival (36.0 months for the gemcitabine group and 39.9 months for the surveillance group, $p = 0.693$). The overall survival was 62.3 months for the gemcitabine group and 63.8 months for the surveillance group ($p = 0.964$). Results of these two studies suggest that gemcitabine-based chemotherapy might not play a significant role in postoperative adjuvant therapy. However, confirmation is needed regarding ongoing phase III studies on gemcitabine-cisplatin combination therapy. The BILCAP study conducted in the United Kingdom compared a group of 447 patients with resected bile duct cancer (intrahepatic, extrahepatic, and muscle-invasive gallbladder cancer) who received capecitabine (1,250 mg/m^2, twice daily, days 1–14, every 3 weeks for a total of 8 cycles) with a surveillance group [250]. Intention-to-treat analysis showed no statistical significance. However, when analyzed according to the per-protocol plan, the capecitabine group demonstrated a significant improvement in relapse-free survival (24.4 months vs. 17.5 months in the surveillance group, $p = 0.0093$). The overall survival period also showed a significant improvement (53 months in the capecitabine group vs. 36 months in the surveillance group, $p = 0.0028$). Based on these findings, international guidelines currently recommend capecitabine as the standard adjuvant therapy for radically resected bile duct cancer patients.

Radiotherapy

KQ26. Is radiation therapy (chemoradiotherapy) useful in patients with locally recurrent extrahepatic bile duct cancer after resection surgery?

Consider administering (chemoradiotherapy) radiation therapy to patients with locally recurrent extrahepatic bile duct cancer after resection surgery (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

There have been four retrospective studies reporting on the role of radiation therapy in patients with locally recurrent extrahepatic bile duct cancer after resection surgery [251-254]. When chemoradiotherapy was administered, the median overall survival ranged from 16 to 41 months [251-254] and the 1-year local control rate ranged from 59% to 67% [251,252]. Grade 3 or higher gastrointestinal side effects were either absent [251,253] or reported in less than 3% [252]. It has been reported that administering chemoradiotherapy could increase progression-free survival [251,252] or overall survival compared to radiation therapy alone [252]. Moreover, when the biologically effective dose exceeded 59 Gy, it could lead to improved local control rates and overall survival compared to cases where the dose was below 59 Gy [252].

KQ27. Is radiation therapy after radical resection surgery useful in patients with extrahepatic bile duct cancer?

Consider administering adjuvant chemoradiotherapy after radical resection surgery in patients with extrahepatic bile duct cancer (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	II. Moderate

It is recommended to consider administering adjuvant chemoradiotherapy when the resection margin is R1 after radical resection surgery in patients with extrahepatic bile duct cancer (Grade A).

Recommendation grade	A. Strong recommendation
Level of evidence	II. Moderate

Studies have compared treatment outcomes based on the administration of adjuvant (chemo)radiation therapy after radical resection surgery for extrahepatic bile duct cancer. These studies included eight retrospective studies [255-261] and three meta-analyses [262-264].

The eight retrospective studies included single-center publications from South Korea [255,256], a single-center publication from Japan [257,258], and a research analysis using data from the National Cancer Database (NCDB) in the United States [259-261]. Additionally, a multicenter retrospective study in South Korea involving a large number of patients was recently published.

Initially, studies were primarily focused on evaluating the efficacy of postoperative radiation therapy in patients with positive resection margins. Gwak and colleagues reported that the median disease-free survival increased from 10 months to 21 months when postoperative radiation therapy was administered in patients with positive resection margins [251].

Todoroki and colleagues [253] reported that postoperative radiation therapy in patients with perihilar extrahepatic bile duct cancer extended the median overall survival from 10 months to 32 months. Similarly [257], Kobayashi and colleagues observed that postoperative radiation therapy for patients with perihilar extrahepatic bile duct cancer with resection margins of 5 mm or less or positive resection margins increased the 3-year overall survival rate from 23% to 47% [254].

Recently, studies have expanded beyond the scope of patients with positive resection margins. They have included a relatively large number of patients. Among these studies, Chang and colleagues [252] conducted a multivariate analysis on 328 patients with extrahepatic bile duct cancer located proximal to hepatic duct confluence, excluding perihilar bile duct cancer. Their analysis confirmed that postoperative chemoradiotherapy was an independent prognostic factor for disease-free survival and overall survival [252].

In the United States, numerous studies have reported effects of postoperative (chemo)radiotherapy based on data from the NCDB. Among these studies, Hoehn and colleagues conducted an analysis focusing on patients with perihilar and proximal extrahepatic bile duct cancer [255]. Nassour and colleagues have concentrated on patients with proximal extrahepatic bile duct cancer [256]. Additionally, Kamarajah and colleagues have analyzed patients with distal extrahepatic bile duct cancer [257]. All three studies confirmed that postoperative (chemo) radiotherapy significantly improved overall survival compared to surgery alone, irrespective of the margin status. Particularly, Hoehn and Kamarajah reported that postoperative (chemo) radiotherapy had benefits regardless of the margin status [255,257].

The most recent analysis involved 1,475 patients with perihilar extrahepatic bile duct cancer who underwent radical surgery at 14 different institutions in South Korea. Results indicated that patients who received postoperative (chemo)radiotherapy experienced significant improvements in disease-free survival and overall survival regardless of the presence of positive margins or lymph node involvement.

Three separate meta-analyses were conducted, each focusing exclusively on retrospective observational studies of patients with extrahepatic bile duct cancer, excluding cases of intrahepatic bile duct cancer, gallbladder cancer, and pancreatic head cancer. These meta-analyses comprising 10 [262], 8 [263], and 23 [264] papers, respectively, reported that postoperative (chemo)radiotherapy was associated with a statistically significant increase in overall survival compared to surgery alone.

Several studies have demonstrated a decrease in local recurrence rate following postoperative (chemo)radiotherapy. For example, Gwak and colleagues reported that in patients with positive margins who received postoperative radiotherapy, local recurrence rates decreased from 61.7% to 35.6% [251]. Todoroki and others confirmed a reduction in local recurrence rate from 68.8% to 20.8% in patients who underwent postoperative radiotherapy [253].

Kim's study [258] indicated that not only patients with positive margins, but also those with negative margins and negative lymph nodes experienced significantly lower local recurrence rates when treated with postoperative (chemo)radiotherapy.

Unresectable cases

Diagnosis & biliary drainage

KQ28. What are recommended diagnostic methods for patients with unresectable extrahepatic bile duct cancer?

In patients with unresectable extrahepatic bile duct cancer, it is recommended to perform a combination of endoscopic biopsy tissue examination and brush cytology for pathological diagnosis (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

Pathological diagnosis in patients with unresectable extrahepatic bile duct cancer has mainly been studied through retrospective research. Randomized controlled trials comparing diagnostic methods are lacking, making it difficult to establish clear evidence for one diagnostic method over another. In cases of unresectable extrahepatic bile duct cancer, a diagnosis can sometimes be made based on clinical findings through imag-

ing diagnostic methods when there are clear signs. However, in many cases, the test for pathological diagnosis is essential when making a diagnosis and determining treatment plans.

There are several methods for pathological diagnosis of extrahepatic bile duct cancer, including brush cytology via retrograde cholangiopancreatography and FNA with tissue examination using endoscopic ultrasound [265]. Among these methods, brush cytology using endoscopy has the advantage of relatively higher diagnostic accuracy [266]. However, using a single method may have limitations [267]. Combining different diagnostic methods can improve accuracy [268-270]. Brush cytology has the advantage of not requiring significant additional resources or costs [59]. Endoscopic ultrasound-based examinations have lower diagnostic accuracy than other methods mentioned above. They are generally not preferred due to potential complications [54,269,271]. Using the PTBD approach for brush cytology can achieve a sensitivity of 78%. However, it comes with a high false-positive rate (22%–29%), making it challenging to completely rule out malignant bile duct obstruction even when results are negative [272].

In cases of unresectable extrahepatic bile duct cancer, there are two main methods for pathological diagnosis: direct POC using a peroral upper gastrointestinal endoscope and the SpyGlass system (SpyGlass Direct Visualization System) [273,274]. Direct POC has the advantage of being able to visually observe the lesion directly and collect tissue samples from the desired area. However, when it comes to observing the upper part of the bile duct, maintaining the position of the endoscope can be challenging, making it less effective for proximal bile duct observation. Additionally, if the cause of bile duct obstruction originates from outside the bile duct, the accuracy of tissue sampling may significantly decrease, which is a limitation of this method. On the other hand, reported diagnostic sensitivity and accuracy of SpyGlass system-guided cholangioscopy are 76.5%–88.0% and 77.0%–90.0%, respectively.

Compared to tissue sampling through ERCP-guided cholangioscopy, direct POC showed a sensitivity of 92.3% and a diagnostic accuracy of 93.6% in diagnosing malignancy among 32 patients where malignancy was not detected [275-279]. However, very few prospective comparative studies are available to provide robust evidence regarding the superiority of one method over the other.

When performing tissue sampling through ERCP, there is a risk of complications associated with the procedure, which can lead to cholangitis. This could potentially impact the prognosis of patients with bile duct cancer [63,280]. However unresectable extrahepatic bile duct cancer is often associated bile duct obstruction. Therefore, it is not easy to consider that the additional performance of biliary drainage procedures for pathological diagnosis increases the risk of cholangitis [281,282].

Therefore, when considering diagnostic methods for unresectable extrahepatic bile duct cancer, a combination of endoscopic choledochoscopy tissue examination and brushing cytology using an endoscope is primarily recommended.

KQ29. What is the effective method for bile duct drainage in unresectable proximal extrahepatic bile duct cancer?

In cases where bile duct drainage is necessary for unresectable proximal extrahepatic bile duct cancer, consider endoscopic bile duct drainage using a metal stent (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	III. Low

Research on drainage procedures in patients with unresectable malignant distal bile duct obstruction has been systematically and comprehensively conducted. However, studies focusing exclusively on bile duct cancer patients are scarce. In existing research, the majority of causes of malignant distal bile duct obstruction were pancreatic cancer, while approximately one-fourth resulted from bile duct cancer. Regarding patients' quality of life, a prospective cohort study involving unresectable malignant bile duct obstruction patients found significant improvement in social functioning (RR = 0.11, 95% CI: 0.03–0.19) and mental health (RR = 0.036, 95% CI: 0.011–0.08) after endoscopic drainage [283].

In retrospective studies of patients with unresectable malignant distal bile duct obstruction, it has been reported that endoscopic drainage with metal stents, when necessary, can result in a shorter hospital stay (14 days vs. 8 days, $p = 0.001$) and a lower complication rate (67% vs. 31%, $p = 0.00002$) compared to performing preventive bypass surgery [284]. Randomized comparisons of endoscopic drainage and surgical bypass surgery in patients with unresectable malignant distal bile duct obstruction showed no significant difference in patient survival or complication rate [285].

Randomized comparative studies or meta-analyses comparing endoscopic drainage and PTBD in malignant bile duct obstruction had limitations due to predominant occurrence of distal bile duct obstruction at the ampullary level. Although PTBD showed an advantage in terms of treatment success, it did not demonstrate difference in 30-day survival or complication rate [286,287]. To date, a proper comparative analysis between the two procedures in malignant distal bile duct obstruction has not been adequately conducted [286,287].

Several randomized controlled trials and meta-analyses comparing the effectiveness of plastic stents and metal stents in patients with inoperable bile duct obstruction have been conducted. However, studies exclusively involving bile duct cancer patients have not been reported yet. Most studies included a substantial number of pancreatic cancer patients, which had several limitations. Nevertheless, metal stents were found to be beneficial [288-291]. In meta-analyses, when stents were inserted endoscopically or percutaneously, metal stents were superior in terms of stent patency, with an approximately 4.45-month

advantage (95% CI: 0.31–8.59). However, there were no significant differences in overall survival or 30-day survival rate between the two groups. It was worth noting that this study included patients with distal bile duct obstruction, which might not be directly applicable to lower bile duct obstruction [288]. In a randomized controlled study specifically targeting patients with lower bile duct obstruction, the patency duration of metal stents was significantly longer, lasting 273 days compared to 126 days for plastic stents ($p = 0.006$). However, that study did not include patients with bile duct cancer. It was focused solely on pancreatic cancer and periampullary tumors, which was a limitation [289].

On the other hand, results were different when comparing covered and uncovered metal stents in randomized controlled studies and meta-analyses [292-297]. In a randomized controlled study where percutaneous stent insertion was performed only for patients with CBD tumors, the patency duration of covered stents (179.5 days) was significantly longer than that of uncovered stents (133.1 days) ($p = 0.002$). Complication rates were similar between covered and uncovered stents. However, patients' survival duration showed a significant advantage for covered stents (243.5 days) compared to uncovered stents (180.5 days) ($p < 0.05$) [294]. Other randomized controlled studies also showed that covered stents were superior to uncovered stents in terms of stent occlusion and patency. However, subgroup analysis revealed no significant occlusion between covered and uncovered stents for patients with bile duct cancer [292]. Remaining studies did not show any significant occlusion and potency either between covered and uncovered stents [292,293,295,296].

In a randomized controlled study comparing fully covered metal stents of different diameters (8 mm and 10 mm) in patients with inoperable malignant lower bile duct obstruction, there were no significant differences in patient survival, adverse events, or bile duct obstruction recurrence rates [298].

In a randomized controlled study comparing the effectiveness of metal stents with anti-reflux valves to reduce bile duct obstruction in patients with inoperable malignant lower bile duct obstruction, patient survival and adverse event rates in the group receiving metal stents with anti-reflux valves were similar to those receiving conventional metal stents. However, the duration of bile duct patency was superior when using stents with anti-reflux valves (407 days vs. 220 days, $p = 0.013$) [299]. However, that study was a small-scale pilot study conducted at a single institution. Further research is needed to generalize its results [299].

Contrasting results seen in various studies can be attributed to the lack of standardized criteria for evaluating the efficacy of bile duct drainage [300]. The utilization of standardized evaluation methods, such as the Tokyo criteria proposed in Japan, is expected to facilitate more straightforward meta-analyses and yield more precise results [301]. Moreover, it is necessary to establish standardized criteria tailored to the domestic context in South Korea.

Recently, in cases where ERCP is challenging, ultrasound-guided PTBD is being attempted as an alternative to PTBD [302]. In a multicenter prospective study, ultrasound-guided PTBD demonstrated a technical success rate of 95.8% and a clinical success rate of 89.5%. Rate of complications reported was 10.5%, indicating that this approach, when performed by experts, could be a relatively safe as an effective alternative [303].

In a randomized controlled study comparing the effectiveness of PTBD and ultrasound-guided biliary drainage in patients with inoperable malignant lower bile duct obstruction, there were no significant differences in success rate or quality of life [304]. Additionally, in another study, the group undergoing ultrasound-guided biliary drainage had a lower rate of complications [305].

In a randomized controlled study conducted in South Korea on patients with inoperable malignant lower bile duct obstruction to compare the effectiveness of ERCP with ultrasound-guided biliary drainage, both groups had similar technical and clinical success rates. However, the ultrasound-guided group had stent dislocation in 2 cases and stent blockage due to debris in 6 cases. In the ERCP group, stent blockage due to tumors was observed in 9 cases. The ERCP group had a higher incidence of complications such as pancreatitis (19.7% vs. 6.3%, $p = 0.03$) and required more repeat procedures (42.6% vs. 15.6%, $p = 0.001$) [306].

KQ30. In cases of unresectable perihilar cholangiocarcinoma, what is an effective biliary drainage procedure?

In cases of unresectable perihilar cholangiocarcinoma requiring biliary drainage, plastic or metal stent-based biliary drainage procedures are considered (Grade A).

Recommendation grade	A. Strong recommendation
Level of evidence	II. Moderate

Studies comparing effects of ERCP and PTBD in perihilar cholangiocarcinoma are rare. Therefore, the choice of biliary drainage method often depends on the physician's experience and proficiency as well as facilities available at the hospital. Generally, in Bismuth type I-II perihilar cholangiocarcinoma cases requiring biliary drainage, ERCP is preferred over PTBD [307,308]. However, there is a debate over the appropriate biliary drainage method for Bismuth type III-IV perihilar cholangiocarcinoma. Moole et al. [309] have conducted a meta-analysis of five retrospective studies comparing PTBD and ERCP and reported that PTBD is more effective in draining bile (OR: 4.94, 95% CI: 2.09 to 11.72). In that study, the overall frequency of complications, including cholangitis and pancreatitis, did not differ significantly between the two methods. However, PTBD was associated with a higher risk of postprocedure

bleeding (OR: 5.39, 95% CI: 1.38 to 21.15). Coelen et al. [310] have conducted a multicenter randomized study comparing ERCP and PTBD in resectable perihilar cholangiocarcinoma. However, they had to terminate the study early due to a higher mortality rate in the PTBD group. On the other hand, recently published studies on biliary drainage using ERCP in perihilar cholangiocarcinoma showed success rates of over 85% [311,312]. For effective biliary drainage, it is crucial to select non-obstructed bile ducts in the hepatic parenchyma without inflammation [313]. However, in the case of Bismuth type III-IV perihilar cholangiocarcinoma where both right and left hepatic ducts along with their branches are often obstructed, the choice of the appropriate drainage method (such as ERCP or PTBD) should be determined based on the patient's condition, including factors such as the extent of tumor invasion, anatomical changes due to previous surgeries, the presence of multiple lesions, and other relevant factors.

Randomized controlled studies comparing effects of plastic stents and metal stents used in ERCP for unresectable perihilar cholangiocarcinoma patients have been reported. Three of them demonstrated that metal stents were superior to plastic stents in terms of bile drainage effectiveness [314] with a longer patency period. Although metal stents have higher cost than platic stents, they are more cost-effective due to a reduced need for reintervention [315]. These results were consistent with findings of three retrospective studies [316-318].

A prospective study by Perdue et al. [319] comparing complications within 30 days found that plastic stents were associated with a higher rate of complications including cholangitis, stent occlusion, migration, perforation, and additional drainage procedures (either endoscopic or percutaneous) (32% vs. 9%, $p = 0.027$). However, in a multicenter retrospective study by Choi et al. [320], the time between plastic stent insertion and performing percutaneous drainage was longer (836.43 days vs. 586.40 days, $p = 0.039$). In a prospective study by Iwasaki et al. [321], although plastic stents resulted in a shorter patency period (66 days vs. 105 days, $p = 0.04$), plastic stents had a higher success rate for reintervention using endoscopy (96.5% vs. 55%, $p = 0.0002$).

There is a debate regarding whether bilateral drainage is necessary in patients with perihilar cholangiocarcinoma.

A randomized controlled study conducted by Lee et al. [312] compared endoscopic biliary drainage with metal stents. It found that bilateral drainage and unilateral drainage had similar technical success rates. However, bilateral drainage had a longer patency period and a lower need for reintervention than unilateral drainage. On the other hand, in a randomized controlled study by Hakuta et al. [322], there was no significant difference between bilateral drainage and unilateral drainage groups of patients who underwent endoscopic biliary drainage with metal stents. A meta-analysis study of two randomized controlled studies and five retrospective studies reported that bilateral biliary drainage with metal stents during endoscopic biliary drainage had a significantly lower reintervention rate than unilateral drainage (OR: 0.59, 95% CI: 0.40–0.87, $p = 0.009$). However, technical success and complication rates were similar between the two groups. Two retrospective studies comparing plastic stents, metal stents, bilateral drainage, and unilateral drainage in endoscopic biliary drainage found that bilateral drainage with metal stents had the best outcomes [323,324].

On the other hand, in a meta-analysis study regarding percutaneous drainage, there were no significant differences in technical success rates, drainage effectiveness, complications, or survival periods between bilateral drainage with metal stents and unilateral drainage [315].

Furthermore, a study by Vienne et al. [325] using CT volumetry reported an increased survival rate when more than 50% of the total liver volume was drained (119 days vs. 59 days, $p = 0.005$).

Studies comparing covered and uncovered metal stents in endoscopic biliary drainage for perihilar cholangiocarcinoma patients have not been reported yet. All studies except one used uncovered metal stents. Yoshida et al. [326] have inserted 6 mm diameter uncovered metal stents side by side to prevent stent occlusion due to tumor and facilitate reintervention. They achieved a high technical success rate and effective bile drainage, but reported gallbladder inflammation in 3% and liver abscess in 7% of cases.

In contrast, a retrospective study by Shim et al. [314] on percutaneous drainage compared bilateral drainage, unilateral drainage, covered, and uncovered metal stents. There were no significant differences in success rates, complications, survival periods, or stent patency between groups. In endoscopic biliary drainage using metal stents, meta-analysis studies and randomized controlled studies consistently found no significant differences between side-by-side and stent-in-stent methods [327].

Recently, there has been an increasing trend in performing ultrasound-guided biliary drainage procedures as an alternative to ERCP. In two retrospective studies on patients with unresectable perihilar cholangiocarcinoma for whom ERCP failed or was not feasible, the technical success rate of ultrasound-guided biliary drainage was over 90%, with effective biliary drainage achieved in over 70% of cases [328,329].

In a study by Minaga et al. [329], there were no procedure-related deaths. However, in a study by Moryoussef et al. [328], one (5.6%) patient died due to bleeding at the procedure site. Additionally, Kongkam et al. [330] conducted a prospective multicenter study comparing a group of patients who underwent a combination of ERCP/ultrasound-guided biliary drainage with a group that underwent percutaneous biliary drainage. They found that the ERCP group had fewer instances of biliary obstruction. However, complication and mortality rates were similar between the two groups.

Chemotherapy

KQ31. Can palliative (first-line) chemotherapy be recommended for patients with localized or metastatic bile duct cancer?

In cases of locally advanced or metastatic extrahepatic bile duct cancer where palliative (first-line) chemotherapy has been administered and the disease has progressed, palliative(second-line) cytotoxic chemotherapy is recommended (Grade A).

Recommendation grade	A. Strong recommendation
Level of evidence	I. High

A recent randomized, multicenter phase 3 study known as the ABC-06 study conducted in the United Kingdom compared patients with advanced bile duct cancer who had experienced progression after initial gemcitabine/cisplatin combination therapy. One group received FOLFOX combination therapy, while the other group underwent aggressive symptom control only. Results demonstrated that the FOLFOX treatment group had an extended overall survival of 6.2 months compared to 5.3 months in the symptom control group (HR: 0.69, $p = 0.031$) [331]. These findings have led to the current recommendation in guidelines for FOLFOX as a second-line treatment for patients with bile duct cancer who have failed initial gemcitabine/cisplatin therapy. However, the improvement in the median overall survival was less than one month in that study. In addition, the study had a primary goal of evaluating progression-free survival. Furthermore, it utilized longer intervals of three months for response assessment, which was longer than the typical 6–8 weeks. These factors suggest that cytotoxic chemotherapy is more effective than a conservative approach. However, further research is necessary to determine whether FOLFOX therapy is the optimal choice.

In a prospective randomized phase 2 study conducted by Choi and colleagues in South Korea, the effectiveness of FOLFOX was compared with that of FOLFIRI as second-line chemotherapy for 120 patients with bile duct cancer. The 6-month survival rate did not show a significant difference (54.1% for the FOLFOX group and 44.1% for the FOLFIRI group, $p = 0.677$) [332]. Another South Korean study, known as the NIFTY study, involved a relatively large-scale prospective phase 2b study comparing liposomal irinotecan, a combination therapy with 5-FU/leucovorin, against 5-FU/leucovorin as a second-line therapy in patients with advanced bile duct cancer [333]. The primary endpoint of progression-free survival was significantly extended in the liposomal irinotecan, 5-FU/leucovorin group, with a duration of 7.1 months compared to 1.4 months in the 5-FU/leucovorin group (HR: 0.56, $p = 0.0019$). The overall survival period also exhibited a meaningful extension, with the liposomal irinotecan, 5-FU/leucovorin group reaching 8.5 months compared to 5.5 months in the 5-FU/leucovorin group (HR: 0.68, $p = 0.0349$). This study suggested the potential for liposomal irinotecan and 5-FU/leucovorin as a second-line therapy.

KQ32. Can palliative (second-line) chemotherapy be recommended for localized or metastatic bile duct cancer?

For patients with localized or metastatic extrahepatic bile duct cancer who have received palliative (first-line) chemotherapy, it is recommended to consider targeted therapy as a second-line treatment if they are appropriate candidates for it (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	II. Moderate

A phase 3 study was conducted on patients with advanced cholangiocarcinoma who had previously failed treatment with IDH-1 mutations. It compared the IDH-1 inhibitor ivosidenib with a placebo in a randomized 2:1 allocation and found that the progression-free survival was 2.7 months in the Ivosidenib group and 1.4 months in the placebo group, showing a significant difference (HR = 0.37, $p < 0.0001$). However, when it comes to overall survival, the Ivosidenib group had a longer survival time of 10.8 months than the placebo group at 9.7 months, although this difference did not reach statistical significance (HR = 0.69, $p = 0.06$) [334,335]. In this study, when patients with IDH-1 mutations were assigned to the placebo group and their tumors progressed, they were allowed to switch to the active treatment. This allowance for treatment switching was interpreted as having an impact on survival outcomes. Considering this, the recent approval by the U.S. FDA allows the use of ivosidenib as a second-line treatment for advanced cholangiocarcinoma patients who have previously failed treatment with IDH-1 mutations.

Pemigatinib, another targeted therapy, exhibited a response rate of 35.5% in a phase 2 study involving 146 patients with locally advanced or metastatic cholangiocarcinoma who had FGFR2 fusion or rearrangement [336]. Infigratinib administered as a second-line treatment to 122 patients with FGFR2 fusion or rearrangement-positive locally advanced or metastatic cholangiocarcinoma demonstrated a response rate of 23.1% [337]. While these studies were single-arm phase 2 trials, they presented promising response rates compared to traditional second-line therapies and exhibited a manageable toxicity profile. These findings suggest that FGFR inhibitors may be appropriate second-line treatments for cholangiocarcinoma patients with FGFR2 gene fusion/rearrangement. Based on these results, the U.S. FDA has granted accelerated approvals for pemigatinib and infigratinib. The UK's NICE has also approved them for treating patients with FGFR2 gene fusion/rearrangement. However, these treatments have not yet been approved for use in South Korea.

In the case of pembrolizumab, when 24 and 104 patients with advanced cholangiocarcinoma included in KEYNOTE-028 and KEYNOTE-158 studies, respectively, were analyzed separately, the overall survival was 5.7 months and the progression-free survival was 1.8 months in KEYNOTE-028. In KEYNOTE-158, the overall survival was 7.4 months and the progression-free survival was 2.0 months. The response rate for patients with PD-L1 expression was 6.6% (4 out of 61 patients). For those without PD-L1 expression, it was 2.9% (1 out of 34 patients) [338]. In a retrospective analysis in South Korea, among 40 patients with advanced or metastatic biliary tract cancer who were PD-L1 positive, the median progression-free survival was 1.5 months and the median overall survival was 4.3 months, showing similar results to other second-line treatments [339]. Pembrolizumab is currently approved as a second-line therapy with expedited approval. However, there is no clear biomarker to predict its effectiveness in patients. It may be recommended for patients with a certain degree of efficacy, such as those with high microsatellite instability.

Nivolumab, on the other hand, showed promising results in a phase 2 study that included 54 patients with advanced or metastatic biliary tract cancer. That study reported a median overall survival of 14.2 months and a median progression-free survival of 3.6 months. The objective response rate was 22% and the independent response rate was 11%. As a result, it has received pre-approval status for use [340].

Radiotherapy

KQ33. Is radiation therapy beneficial for patients with unresectable extrahepatic bile duct cancer?

Radiation therapy is considered for patients with unresectable extrahepatic bile duct cancer (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	II. Moderate

In patients with unresectable extrahepatic bile duct cancer, radiation therapy is considered for some patients due to the need for local control of the primary lesion. Various treatment methods, including brachytherapy and external beam radiation therapy, combined with chemotherapy, have been reported. Randomized phase III studies are rare in this clinical scenario. A total of 6 studies were identified after applying selection and exclusion criteria. These six sudies inlcuded one randomized phase II study, four studies based on large-scale patient data from the United States, specifically Surveillance, Epidemiology, and End Results (SEER) and NCDB data, and one small-scale retrospective comparative study [151,341-345].

The randomized phase II study included patients with unresectable locally advanced extrahepatic bile duct cancer. It compared a group that received gemcitabine/oxaliplatin combination therapy for a total of 12 cycles every 2 weeks (chemotherapy) with a group that received external beam radiation therapy administered concurrently with 5-FU/cisplatin over 25 fractions for a total radiation dose of 50 gray (Gy) (concurrent chemoradiation therapy [CCRT] group - no further adjuvant therapy allowed). Although the study aimed to enroll a total of 72 patients, it was prematurely terminated after enrolling 34 patients. In terms of grade 3–4 toxicities, the CCRT group showed a rate of 47%, and the chemotherapy group showed a rate of 75%. Biliary complications were observed in 28% of the CCRT group and 44% of the chemotherapy group. While the chemotherapy group tended to show better progression-free and overall survival rates than the CCRT group, their differences were not statistically significant [341]. However, the study did not meet its enrollment goal. The limited number of patients may require caution when interpreting its results.

In four large-scale patient data-based studies, although there were slight differences in the specific radiation therapy method employed, they primarily analyzed treatment outcomes based on whether radiation therapy was administered to patients with unresectable bile duct cancer, reporting similar results [342-345]. In a study by Pollom and others based on SEER data, when analyzing all patients with unresectable bile duct cancer, benefits of radiation therapy were somewhat limited [339]. However, it showed an improvement in survival rate (median survival: 10 months vs. 9.3 months, $p = 0.02$) [339]. Especially when considering the subgroup of patients who received chemotherapy, the survival benefit of radiation therapy was more pronounced (adjusted HR: 0.82, 95% CI: 0.70–0.97, $p = 0.02$). Torgeson and colleagues [341] have conducted a study based on NCDB data comparing chemotherapy alone with combined chemotherapy and radiation therapy in patients with unresectable bile duct cancer. When analyzing a cohort of 2,996 patients treated from 2004 to 2014, the combined chemotherapy and radiation therapy group had a median survival period of 14.5 months, which was superior to the chemotherapy-alone group at 12.6 months (HR: 0.83, 95% CI: 0.76–0.92, $p < 0.001$) [345]. These results were confirmed even after propensity score matching (HR: 0.85, 95% CI: 0.77–0.95, $p = 0.003$). Shinohara and colleagues have conducted an analysis of clinical outcomes of brachytherapy (including combined external beam radiation therapy) in bile duct cancer patients based on SEER data. The group receiving brachytherapy had a significantly longer median survival period (11 months vs. 4 months, $p < 0.0001$) [340]. In another study by Shinohara and others based on SEER data, the utility of radiation therapy in extrahepatic bile duct cancer patients was investigated. The group that underwent radiation therapy had a significantly longer median survival period than the group that underwent surgery or received no treatment (9 months vs. 4 months, $p < 0.0001$) [335]. Furthermore, in a single-institution study conducted in South Korea, localized advanced bile duct cancer patients who underwent CCRT showed a significantly longer median survival period than to the best

supportive care group (42.57 weeks vs. 13.29 weeks, $p < 0.001$) [151].

KQ34. Is palliative radiotherapy after biliary drainage useful in patients with extrahepatic bile duct cancer?

Palliative radiotherapy after biliary drainage is considered for symptom relief in patients with extrahepatic bile duct cancer (Grade B).

Recommendation grade	B. Conditional recommendation
Level of evidence	II. Moderate

In patients with unresectable extrahepatic bile duct cancer, both percutaneous drainage and endoscopic stent insertion have been widely used for the improvement and prevention of bile duct obstruction symptoms. However, the recurrence rate is high [346]. Three prospective studies have been conducted to assess the improvement of bile drainage maintenance with the addition of radiation therapy, especially brachytherapy. In Valek's study involving 42 patients with bile duct cancer who underwent stent insertion and radiation therapy, an increase in mean survival duration was observed (388 days vs. 298 days) [263]. Subsequently, Jiao's study [264], which included 61 patients with malignant bile duct obstruction who underwent stent insertion, compared effects of additional radiation therapy. The group that received radiation therapy showed significantly improved bile duct patency (368 days vs. 220 days, $p = 0.003$) and survival duration (355 days vs. 209 days, $p = 0.02$) [347]. The most recent study by Zhu involving 328 patients also showed that the addition of radiation therapy after stent insertion reduced the reocclusion rate (9% vs. 15%) and increased survival duration (202 days vs. 140 days, $p = 0.003$) [346]. A systematic review and meta-analysis study that included 641 patients from 12 studies comparing effects of additional radiation therapy after stent insertion found no differences in treatment-related side effects. However, in the group that received brachytherapy, the stent occlusion rate was lower (OR: 0.19, 95% CI: 0.13–0.28, $p < 0.0001$) and the survival rate was higher (MD = 3.15, 95% CI: 2.64–3.66, $p < 0.0001$) [348].

From the perspective of palliative radiotherapy, a retrospective study comparing bypass surgery or nerve blockade and palliative radiotherapy for the control of intractable pain in patients with unresectable peripancreatic lesions reported significant improvement in the duration of pain medication and overall survival [347]. Additionally, a retrospective study by Dowsiriroj and colleagues that focused on patients with vertebral metastases from bile duct cancer reported that the radiotherapy group showed improved survival compared to the surgery group or the conservative treatment group (6 months for radiotherapy, 3 months for surgery, and 2 months for conservative treatment) [349].

Conclusions

Users of the Extrahepatic Bile Duct Cancer Treatment Guidelines are clinical practitioners involved in the treatment of bile duct cancer. Moving forward, continuous generation of essential clinical questions and evidence-based recommendations will be maintained and updates will be made as the evidence evolves. These guidelines have been structured using algorithms to enhance readability. Various strategies for dissemination will be developed to promote the application of these guidelines.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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