

*Jarmo Niemelä*

MALIGNANT BILIARY  
OBSTRUCTION AND  
PERCUTANEOUS  
TRANSHEPATIC BILIARY  
DRAINAGE – THE IMPACT  
OF CHOLANGITIS AND  
CHEMOTHERAPY ON SURVIVAL

UNIVERSITY OF OULU GRADUATE SCHOOL;  
UNIVERSITY OF OULU,  
FACULTY OF MEDICINE;  
MEDICAL RESEARCH CENTER OULU;  
OULU UNIVERSITY HOSPITAL





ACTA UNIVERSITATIS OULUENSIS  
D Medica 1671

*JARMO NIEMELÄ*

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PERCUTANEOUS TRANSHEPATIC  
BILIARY DRAINAGE – THE IMPACT  
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CHEMOTHERAPY ON SURVIVAL**

Academic Dissertation to be presented with the assent of the Doctoral Programme Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium I of Oulu University Hospital (Kajaanintie 50), on 25 May 2022, at 12 noon

UNIVERSITY OF OULU, OULU 2022

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Acta Univ. Oul. D 1671, 2022

Supervised by  
Docent Hannu Syrjälä  
Doctor Raija Kallio

Reviewed by  
Docent Päivi Auvinen  
Docent Ville Sallinen

Opponent  
Professor Juha Grönroos

ISBN 978-952-62-3290-4 (Paperback)  
ISBN 978-952-62-3291-1 (PDF)

ISSN 0355-3221 (Printed)  
ISSN 1796-2234 (Online)

Cover Design  
Raimo Ahonen

PUNAMUSTA  
TAMPERE 2022

## **Niemelä, Jarmo, Malignant biliary obstruction and percutaneous transhepatic biliary drainage – the impact of cholangitis and chemotherapy on survival.**

University of Oulu Graduate School; University of Oulu, Faculty of Medicine; University of Oulu, Faculty of Medicine, Medicine, Medical Research Center Oulu; Oulu University Hospital  
*Acta Univ. Oul. D 1671, 2022*

University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

### ***Abstract***

The purpose of this retrospective study was to clarify the challenging treatment of the patients with malignant biliary obstruction treated with percutaneous transhepatic biliary drainage (PTBD) in a large series of real-life clinical practice. This study consists of all patients who were treated with PTBD for malignant biliary obstruction between 1999 and 2016 at the Oulu University Hospital. Among 643 patients, 258 (40.1%) had pancreatic cancer, 222 (34.5%) had biliary tract cancer, 52 (8.1%) had gastric cancer, 43 (6.7%) had colorectal cancer and 68 (10.6%) had other cancers. This thesis consists of three studies.

Study I evaluated the survival and predictive factors for outcomes of all the patients in this cohort. Patients had a poor prognosis with an overall median survival of 2.6 months after PTBD. Independent factors predicting poor outcome were metastatic cancer, Eastern Cooperative Oncology Group performance status (ECOG PS) >2, American Society of Anesthesiologists (ASA) class 4, and bilirubin level after PTBD  $\geq 60.0 \mu\text{mol/L}$ .

Study II evaluated the impact of cholangitis on survival in 588 patients with gastrointestinal cancer: 158 patients with cholangitis before PTBD had poorer survival (1.8 months) than 215 patients with cholangitis after PTBD (3.0 months).

Study III evaluated the survival benefit of chemotherapy compared to best supportive care after PTBD for patients with pancreatic or biliary tract cancer: 32 patients with pancreatic or biliary tract cancer that received chemotherapy showed significantly better survival (11.7 months) than 126 patients that received only the best supportive care (1.7 months).

Patients with cancer and biliary obstruction treated with PTBD have a poor prognosis. The results of this study highlight a systematic need for oncologic evaluation of patients after PTBD, because chemotherapy after PTBD was associated with several months of survival benefit compared to patients with only best supportive care. Treatment of cholangitis with biliary drainage in addition to antimicrobial treatment is crucial for improving survival. The found predictive factors (metastatic cancer, ECOG PS, ASA class, cholangitis, and bilirubin level after drainage) should be taken into account when a multidisciplinary team evaluate appropriate treatment for these challenging patients.

***Keywords:*** biliary obstruction, cancer, chemotherapy, cholangitis, percutaneous transhepatic biliary drainage, survival



## **Niemelä, Jarmo, Syövän aiheuttaman sappitien tukoksen hoito ihon ja maksan lävitse tehtävällä sappitien kanavoinnilla — sappitien tulehduksen ja solunsalpaajahoidon vaikutus ennusteeseen.**

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Oulun yliopisto, Lääketieteellinen tiedekunta, Lääketiede, Medical Research Center Oulu; Oulun yliopistollinen sairaala

*Acta Univ. Oul. D 1671, 2022*

Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

### ***Tiivistelmä***

Tällä taannehtivalla tutkimuksella kartoitettiin syövän aiheuttaman sappitien tukoksen hoitoa ihon ja maksan lävitse tehtävällä sappitien kanavoinnilla (PTBD). Tutkimuksessa olivat mukana kaikki PTBD:llä vuosina 1999–2016 Oulun yliopistollisessa sairaalassa syövän aiheuttaman sappitien tukoksen vuoksi hoidetut 643 potilasta. Heistä 258 potilaalla (40,1 %) oli haimasyöpä, 222 potilaalla (34,5 %) sappitiesyöpä, 52 potilaalla (8,1 %) mahasyöpä, 43 potilaalla (6,7 %) paksusuolensyöpä ja 68 potilaalla (10,6 %) muita syöpiä. Tämä väitöskirjatyö koostuu kolmesta osatyöstä.

Ensimmäisessä osatyössä selvitettiin koko aineiston potilaiden ennustetta ja siihen vaikuttavia tekijöitä. Heidän mediaani elinaika oli 2,6 kuukautta PTBD:n laiton jälkeen. Itsenäisinä tekijöinä huonompaan ennusteeseen liittyivät etäpesäkkeen aiheuttama sappitien tukos, ECOG:n mukainen suorituskykyluokka 2 tai enemmän, korkea ASA luokka 4 ja bilirubiinin taso yli 60,0 µmol/L PTBD:n jälkeen.

Toisessa osatyössä selvitettiin sappitien tulehduksen vaikutusta ennusteeseen 588 potilaalla, joilla oli ruoansulatuskanavan syöpä. Ennuste oli huonompi 158 potilaalla, joilla todettiin sappitien tulehdus ennen PTBD:tä (1,8 kuukautta) kuin 215 potilaalla, joilla todettiin sappitien tulehdus PTBD:n jälkeen (3,0 kuukautta).

Kolmannessa osatyössä selvitettiin PTBD:n jälkeisen solunsalpaajahoidon vaikutusta eloonjäämiseen 32 haima- ja sappitiesyöpää sairastavalla potilaalla. Solunsalpaajahoidon saaneella potilaalla oli merkittävästi parempi ennuste (11,7 kuukautta) kuin 126 oireenmukaista hoitoa saaneella potilaalla (1,7 kuukautta).

PTBD:llä hoidetun syövän aiheuttaman sappitien tukoksen ennuste on yleensä huono. Tämän tutkimuksen tulokset korostavat potilaiden onkologisen hoidon systemaattista arviota, koska solunsalpaajahoidon saaneiden potilaiden ennuste oli selkeästi parempi verrattuna oireenmukaista hoitoa saaneisiin. Ennusteen parantamiseksi sappitien tulehduksen hoito tukoksen laukaisulla ja antibioottihoidolla on tärkeää. Tutkimuksen ennusteelliset tekijät (ECOG:n mukainen suorituskyky, ASA-luokka, sappitien tulehdus, etäpesäkkeen aiheuttama sappitien tukos ja onnistunut tukoksen hoito) tulee ottaa huomioon, kun potilaiden hoitoa suunnitellaan moniammatillisessa hoitopalaverissa.

*Asiasanat:* ennuste, ihon lävitse tehtävä sappitien kanavointi, sappitien tukos, sappitien tulehdus, solunsalpaajahoido, syöpä



*To my Family*



## Acknowledgements

This doctoral thesis was carried out in the Department of Surgery, the Department of Oncology, the Department of Radiology and the Department of Infection Control during the years 2012 to 2022.

I wish to express my deepest gratitude to my main supervisor of the thesis, Docent Hannu Syrjälä, M.D., Ph.D., for his patience, supportive and encouraging guidance during these years. I respect his profound knowledge and experience in the field of research and the clinical experience that has helped me to complete this research project. I wish to express my gratitude to Raija Kallio, M.D., Ph.D., for supervising the work and sharing her profound knowledge and experience in the field of research and oncology, and for her support and encouragement. I want to express my warm thanks to Professor Juha Saarnio, M.D., Ph.D., for his supervising and encouraging attitude toward me both in clinical practice and in scientific work, all these years. I profoundly respect his extensive clinical experience and skill and passionate attitude towards research. I warmly thank my co-author Docent Jukka Perälä, M.D., Ph.D., for his guidance and support during the beginning of the thesis with his extensive experience in the field of research and radiology. I owe deep gratitude to Pasi Ohtonen, M.Sc., for his respectable expertise in biostatistics and assistance in the statistical analyses. I warmly thank Katri Pauna for processing the patient data for statistical analyses. I want to also thank Aaron Bergdahl, M.Sc., for the language checking of this thesis.

I am grateful to the reviewers of the thesis, Docent Päivi Auvinen, M.D., Ph.D., and Docent Ville Sallinen, M.D., Ph.D., for their valuable and constructive comments, which helped me to improve the quality of this thesis.

I warmly thanks Professor Jyrki Mäkelä, M.D., Ph.D., for his advice, encouragement, positive attitude and support as chairman of the follow-up group in the University of Oulu Graduate School.

I want to express my warm thanks to Professor Tero Rautio, M.D., Ph.D., the Head of the Department of Gastrointestinal Surgery, for his encouragement and positive attitude towards my clinical and research work, also for his advice as a member of the follow-up group.

I thank the Docent, Heikki Wiik, M.D., Ph.D., the Head of the Department of Gastroenterological, Vascular and Urological Surgery, for providing me an opportunity to work and do research.

I want to express my warm thanks to all my colleagues in the Department of Gastroenterological Surgery for their support in my scientific and clinical work.

Especially I want to thank my colleagues in the Hepato-pancreato-biliary unit, Docent Heikki Kiviniemi, M.D., Ph.D.; Docent Arto Saarela, M.D., Ph.D.; Jukka Palm, M.D.; Heikki Karjula, M.D., Ph.D.; Sanna Meriläinen, M.D., Ph.D.; Minna Nortunen, M.D., Ph.D.; Marjo Koskela, M.D., Ph.D.; Tellervo Ylimartimo, M.D. and Docent Heikki Huhta, M.D., Ph.D., for their time and being my excellent colleagues. I would also like to kindly and warmly thank the staff of the Department of Surgery, Gastroenterology, Oncology, Infectious Disease and Radiology.

Finally, I owe my deepest gratitude to my dear wife Arjaleena, for her love, patience and encouraging support during these years, and to my beloved children Laura, Hanna and Akseli – my true-life thesis.

*Oulu, March 2022*

*Jarmo Niemelä*

## Abbreviations

ASA	American Society of Anesthesiologists
ASR	age-standardized rate
BCE	before common era
BDS	biodegradable biliary stents
CE	common era
CI	confidence interval
CT	computed tomography
CRP	C-reactive protein
DAG	directed acyclic graph
ECOG PS	Eastern Cooperative Oncology Group performance status
ERCP	endoscopic retrograde cholangiopancreatography
ESMO	European Society for Medical Oncology
EUS	endoscopic ultrasound
EUS-BD	endoscopic ultrasound-guided biliary drainage
HR	hazard ratio
ILN	inferior limit of normal
IQR	interquartile range
MRI	magnetic resonance imaging
MD-CT	multiphase contrast enhanced multidetector-computed tomography
MRCP	magnetic resonance cholangiopancreatography
NCCN	National Comprehensive Cancer Network
PET-CT	positron emission tomography-computed tomography
PTBD	percutaneous transhepatic biliary drainage
PTC	percutaneous transhepatic cholangiography
SEMS	self-expandable metallic stent
TACE	transarterial chemoembolization
TT-INR	thromboplastin time international ratio
SD	standard deviation
SIRT	selective internal radiotherapy
ULN	upper limit of normal
US	ultrasound



## List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

- I Niemelä, J., Kallio, R., Ohtonen, P., Perälä, J., Saarnio, J., & Syrjälä, H. (2018). Is palliative percutaneous drainage for malignant biliary obstruction useful? *World Journal of Surgery*, *42*(9), 2980-2986. <https://doi.org/10.1007/s00268-018-4567-0>
- II Niemelä, J., Kallio, R., Ohtonen, P., Saarnio, J., & Syrjälä, H. Impact of cholangitis on survival of patients with malignant biliary obstruction treated with percutaneous transhepatic biliary drainage. Manuscript.
- III Niemelä, J., Syrjälä, H., Ohtonen, P., Saarnio, J., & Kallio, R. (2021). Chemotherapy improves survival after percutaneous biliary drainage in patients with pancreatic or biliary tract cancer with biliary obstruction. *Anticancer Research*, *41*(6), 2979-2984. <https://doi.org/10.21873/anticancerres.15079>



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# 1 Introduction

Malignant biliary obstruction is a common clinical problem typically arising from pancreatic and biliary tract cancers as well as advanced stages of other gastrointestinal cancers (Ryan, Hong, & Bardeesy, 2014; Valle, 2010; Wagner et al., 2017; Walia, Quevedo, Hobday, Croghan, & Jatoi, 2008). Most of the patients are usually elderly with problems associated with advanced stages of their malignancy, as well as co-morbidities and impaired general health. Moreover, biliary obstruction and hyperbilirubinemia predispose patients to other consequences, like malnutrition and infection.

Endoscopic retrograde cholangiopancreatography (ERCP) is the primary treatment choice for the drainage of biliary obstruction and relieving symptoms. When ERCP is not feasible due to duodenal obstruction or previous surgery that has altered patient anatomy, or when endoscopic drainage has been insufficient or failed, percutaneous transhepatic biliary drainage (PTBD) is a possible treatment option. PTBD is an invasive procedure with a risk of complications, including bleeding, bile leakage, and infections such as cholangitis and sepsis (Tapping, Byass, & Cast, 2011; Uberoi, Das, Moss, & Robertson, 2012). Earlier PTBD studies have focused mainly on the technical aspects and complications of PTBD. In a large cohort study, the 30-day mortality rate was 23.1% after PTBD for patients with unresectable malignant biliary obstruction (Rees et al., 2020). In the studies in which cholangitis has been clearly defined, the overall survival has been a few months for patients with malignant biliary obstruction treated with PTBD (Saluja et al., 2008; Li et al., 2015; Zu et al., 2019). However, in these studies, the impact of cholangitis, per se, on the outcome has not been systematically analyzed.

Oncological treatment is challenging in patients with malignant biliary obstruction (Lamarca, Benafif, Ross, Bridgewater, & Valle 2015; Jansen, Pape, & Utku, 2020) and patients with hyperbilirubinemia have typically been excluded from clinical studies (Valle et al., 2010; Conroy et al., 2011; Vogel et al., 2015). New chemotherapy combinations have improved survival in patients with pancreatic and biliary tract cancer (Valle et al., 2010; Conroy et al., 2011; Kieler et al., 2020). Data are very limited concerning the utility of chemotherapy for patient groups with malignant biliary obstruction treated with PTBD (Afshar et al., 2014; Mahgerefteh, Hubert, Klimov, & Bloom, 2015; Li et al., 2015; Shin et al., 2020).

Treatment of patients with malignant biliary obstruction is challenging. The purpose of our study was to explore the treatment and survival of patients with malignant biliary obstruction treated with PTBD in a large series in clinical practice.



## 2 Review of literature

### 2.1 History

The first anatomical depiction of the liver, gallbladder and biliary tree was made by the ancient Babylonians 2000 years before the common era (BCE), as well as the first description of jaundice and its association with fever (Ashrafian, 2014). Hippocrates (460 BCE–370 BCE) described bile within his theory of humors. Galen (CE 129–CE 216) described a functional association between the liver and gallbladder and postulated that bile is formed in the gallbladder. Avicenna (980–1037) provided the first description of posthepatic jaundice secondary to biliary obstruction in his *Canon of Medicine* 1025 (Ashrafian, 2014; Dalfardi & Mahmoudi Nezhad, 2014). The term “physiology” was first introduced by Jean Fernel (1497–1558); he also described an association between abdominal pain, peritoneal inflammation and jaundice. Thomas Bartholin (1616–1680) was the first to identify that bile is formed by the liver. Albrecht von Haller (1708–1777) re-described the concept of obstructive jaundice. Ludwig Courvoisier (1843–1918) published in 1890 his research observations that palpable gallbladder distension in jaundiced patients was unlikely to be caused by gallstones, known as the Courvoisier law or sign.

Visualization of the biliary tract by puncturing the gallbladder percutaneously was first reported by Burckhardt and Muller in 1921 (Burckhardt & Müller, 1921). Percutaneous transhepatic cholangiography (PTC) was first described 1937 by Huard and Du-Xuan-Hop (Shimizu, Itoi, & Sano, 2018). The method was ignored for many years, since there were serious complications of bile leakage and intraperitoneal bleeding. In 1952, the possibility of PTC was rediscovered by Carter and Saypol demonstrating cholangiography in a patient with obstructive jaundice caused by carcinoma at the hilum of the liver with confirming the diagnosis via autopsy (Carter & Saypol, 1952). Subsequently, several investigators reported the usefulness of PTC in the diagnosis of biliary disease. A substantial development was X-ray television monitoring during the PTC procedure, which was first introduced in 1962 by Glenn and Arner with their research groups (Glenn, Evans, Mujahed, & Thorbjarnarson, 1962; Arner, Hagberg, & Seldinger, 1962). Under the control of television monitoring, the procedure became safer and more accurate. PTC became more popular and a quite valuable radiological examination for the diagnosis of biliary disease in practice with the introduction of the “Chiba needle”

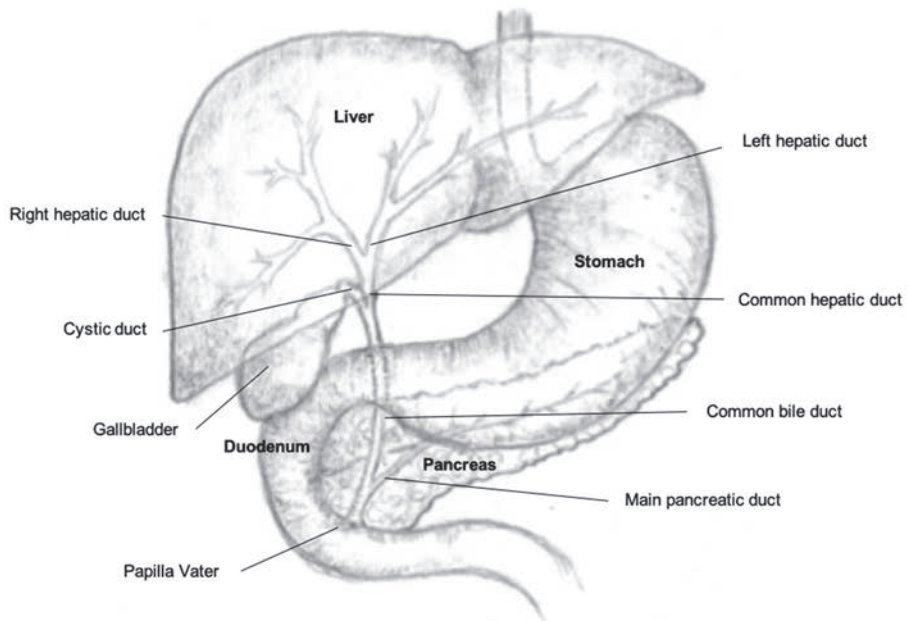
developed at Chiba University in 1969 (Shimizu et al., 2018). This thin and flexible puncture needle reduced the risk of biliary peritonitis and bleeding and improved the success rate of duct opacification. After the first description of catheterization of the bile duct after successful PTC to relieve obstructive jaundice (Glenn et al., 1962), in the 1970s PTC procedures evolved and greatly expanded to clinical applications. Conventional blind puncturing of a bile duct may require multiple passes with a risk of complications, especially if the bile ducts are not dilated. Ultrasound (US) guided PTC was first performed in 1977 (Shimizu et al., 2018). Under US guidance, a needle can be inserted directly and accurately into a suitable peripheral bile duct and thus, PTC has enabled much easier and safer procedures. The use of PTBD for the diagnosis and treatment of obstructive jaundice expanded with wire-guided catheterization across a bile duct stricture providing combined external and internal drainage of bile into the duodenum (Molnar & Stockum, 1974; Nakayama, Ikeda, & Okuda, 1978). ERCP was first introduced in 1968 and with the development of duodenoscopes, use of ERCP expanded in the 1970s (Cotton, 1977). The next achievement in the bile duct drainage was the development of internal stents (Srinivasan & Kahaleh, 2011). An endoscopic plastic biliary stent was first introduced in the late 1970s (Soehendra & Reynders-Frederix, 1979). During the late 1980s, the use of self-expandable metallic stents (SEMS) in biliary strictures inserted in PTBD or ERCP was introduced (Neuhaus, Hagenmuller, & Classen, 1989; Huibregtse, Cheng, Coene, Fockens, & Tytgat, 1989). Endoscopic ultrasound-guided biliary drainage (EUS-BD) was described in the early 2000s (Giovannini et al., 2001). The success rate of mini-invasive procedures has dramatically decreased the need for surgery. Application of percutaneous and endoscopic SEMS have become standard palliative options in the management of malignant biliary obstruction because of their ease and accuracy of placement, high technical and clinical success rates, and high long-term patency rates (Kapoor, Mauri, & Lorenz, 2018). Biodegradable biliary stents (BDS) have been extensively researched and developed in recent years, however, their clinical use is still limited (Siiki, Sand, & Laukkarinen, 2018). The advantage of BDS is mainly from obviating the need for a follow-up procedure to remove the stent. BDS would be particularly useful in settings where there is a need for a stent for only a definite time, such as biliary leak after cholecystectomy, prevention of pancreatitis after ERCP or benign biliary strictures (Mauri et al., 2016; Siiki, Rinta-Kiikka, Sand, & Laukkarinen, 2018; Anderloni et al., 2020; Lindström et al., 2020). Drug-eluting stents with a paclitaxel membrane do not seem to demonstrate any benefit compared to currently available covered SEMS in terms of survival, stent patency

and complications in patients with malignant biliary obstruction (Mohan et al., 2021). Intraluminal brachytherapy in combination with stenting is an effective and safe technique in the management of malignant biliary tract obstruction (Xu, Li, Wu, Zhu, & Ji, 2018; Chen et al., 2021; Taggar et al., 2021). The wider use of intraluminal brachytherapy ablation has been hampered by practical challenges in the implementing of treatment and adverse effects of the therapy (John, Tarnasky, & Kedia, 2021). Endoluminal radiofrequency ablation prior to SEMS may be a promising modality with positive impacts on survival and stent patency in patients with malignant biliary obstruction (Sofi et al., 2018; Gao et al., 2021; Andrasina et al., 2021).

## **2.2 Anatomy of the biliary tract**

Bile is secreted by hepatocytes into bile canaliculi (Suchy, 2016; Waschke, 2019). The canaliculi form a network of polygonal channels between hepatocytes. The canaliculi drain into intralobular bile ducts and coalesce via the interlobular bile duct. These bile ducts anastomose further to form the large hilar, intrahepatic ducts and form the right and left hepatic ducts. The common hepatic duct emerges from the hilum of the liver after the union of the right and left hepatic duct, each of which is 0.5 cm to 2.5 cm long, the left duct is usually longer. The confluence of the right and left hepatic duct occurs outside the liver in approximately 95% of cases; uncommonly, the ducts merge inside the liver, or ducts do not join until the cystic duct joins the right hepatic duct. The common hepatic duct is approximately 3 cm long and is joined by the cystic duct to form the common bile duct. The gallbladder is located in a fossa under the surface of the right lobe of the liver and it is connected to the common hepatic duct via the cystic duct, which is approximately 3 to 4 cm long. The gallbladder is a pear-shaped structure, 3 cm wide and 7 cm long and the volume is 40 to 70 ml. The common bile duct is approximately 7 cm long and usually 0.4 to 0.9 cm in diameter. The common bile duct runs between layers of the lesser omentum in the hepatoduodenal ligament, and lies anterior to the portal vein and to the right of the hepatic artery. The common bile duct passes retroperitoneally behind the first part of the duodenum in a notch on the back of the head of the pancreas and enters the second part of the duodenum. The bile duct joins the main pancreatic duct to form the ampulla of Vater. Eminence duodenal papilla is the mucous membrane bulge produced by the ampulla. In approximately 10% to 15% of the cases, the bile and pancreatic ducts open separately in to the duodenum. As they course through the duodenal wall, the bile and pancreatic ducts are invested

by a thickening of both the longitudinal and circular layers of smooth muscle of the sphincter of Oddi. The bile duct sphincter constricts the lumen of the bile duct and thus prevents bile flow. Contraction of the longitudinal muscle bundles shortens the length of the bile duct and thus promotes the flow of bile into the duodenum. The contraction of the sphincter of the ampulla of Vater shortens the ampulla and approximates the ampullary folds to prevent reflux of intestinal contents into the bile and pancreatic ducts. Anatomy of the biliary tract is illustrated in Figure 1.



**Fig. 1. Anatomy of biliary tract.**

### **2.3 Physiology of bile secretion**

Bile is essential for intestinal lipid digestion and absorption, cholesterol homeostasis, and hepatic excretion of lipid-soluble xenobiotics, drug metabolites,

and heavy metals (Dawson, 2016; Suchy, 2017). The formation of bile occurs in three distinct phases (Suchy, 2017). The bile is secreted into the bile canaliculi by hepatocytes. The intrahepatic and extrahepatic bile ducts secrete into the bile watery, bicarbonate-rich fluid. These phases may produce about 900 mL per day of so-called hepatic bile. Between meals, when the sphincter of Oddi is closed, approximately half of the hepatic bile, about 450 mL, travels to the gallbladder, where the bile is stored and concentrated by absorption of salts and water. The secreted bile that reaches the duodenum is a mixture of “diluted” hepatic bile and “concentrated” gallbladder bile and the volume is about 500 mL per day.

Bile is composed primarily of water, inorganic electrolytes, and organic solutes such as bile acids, phospholipids, cholesterol and bile pigments (Dawson, 2016). The dominant organic components of bile are bile acids, which have multiple functions in the liver and gastrointestinal tract. Most of the bile acids secreted by hepatocytes have been secreted previously into the small intestine, absorbed and have undergone enterohepatic cycling. Bile acids have an important role in the digestion of dietary fats and are essential for the intestinal absorption of cholesterol and fat-soluble vitamins (A, D, E and K). Vitamin K is required by the metabolic processes of the liver for the formation of substances used in coagulation, especially prothrombin and factors VII, IX, X, and protein C (Hall, 2015). In the absence of vitamin K, the concentrations of all these substances decrease markedly and almost prevent blood coagulation. Bile acids play a complex role in the maintenance of cholesterol homeostasis by facilitating the intestinal absorption of biliary and dietary cholesterol and, on the other hand, promote cholesterol elimination from the body (Dawson, 2016). Bile acids also contribute to the bacterial growth in the intestine (Hofmann & Eckmann, 2006; Staley, Weingarden, Khoruts, & Sadowsky, 2017). The excretory or waste products found in bile in addition to cholesterol, bile pigments biliverdin and bilirubin, include trace minerals, plant sterols, lipophilic drugs and metabolites, antigen-antibody complexes, and oxidized glutathione (Suchy, 2017).

Bilirubin is an important metabolite of heme. About 80% of bilirubin is formed from the elimination of excess heme released from senescent red blood cells, with the remainder coming from additional proteins containing heme in other tissues such as skeletal muscle and liver (Barrett & Raybould, 2017). Conversion of heme to bilirubin is a two-stage reaction that takes place in phagocytic cells of the reticuloendothelial system, including Kupffer cells and cells in the spleen. First, iron is released from the heme molecule and produces the green pigment biliverdin, which is then reduced to form yellow, free bilirubin, also called unconjugated

bilirubin. Free bilirubin is bound to albumin and transported through the bloodstream to the liver. In the hepatocytes bilirubin is converted to conjugated bilirubin and the bilirubin conjugates are then secreted into bile.

## **2.4 Jaundice and hyperbilirubinemia**

Hyperbilirubinemia is a condition, in which there is too much bilirubin in the blood. Jaundice, also termed icterus, is a condition of yellow discoloration of body tissues, most notably in the skin and sclera of the eyes (Suchy, 2017). The condition is caused by an accumulation of bilirubin in extracellular fluid, either in free form or after conjugation. In adults, the normal serum bilirubin concentration is lower than 25  $\mu\text{mol/L}$  (Lidofsky, 2016), while jaundice becomes apparent with elevated levels of bilirubin usually higher than 51 to 68  $\mu\text{mol/L}$ , (Korenblat & Berk, 2020).

Hyperbilirubinemia and jaundice can result from an increase in bilirubin production or a decrease in hepatobiliary elimination of bilirubin (Lidofsky, 2016). Increased bilirubin production of hemolysis, ineffective erythropoiesis, or resorption of hematoma may cause unconjugated hyperbilirubinemia. Some drugs such as the antibiotic rifampin and immunosuppressive agent cyclosporine can decrease hepatocellular uptake of bilirubin causing unconjugated hyperbilirubinemia, or it may be caused by decreased conjugation, of which the most common is Gilbert's syndrome. Jaundice is a common feature in liver disease, in which hyperbilirubinemia is usually associated with other biochemical liver test abnormalities. Hepatic dysfunction can be caused by acute or chronic hepatocellular injury resulting from a variety of conditions that include viral hepatitis, exposure to hepatotoxins like ethanol and drugs, ischemia, and certain metabolic derangements such as Wilson disease. Intrahepatic cholestatic disorders are characterized by impaired bile formation in the absence of widespread hepatocellular injury or bile duct obstruction. These kinds of disorders may be due to infiltrative diseases such as injury of cholangiocytes in primary biliary cirrhosis, drugs and infections. These disorders with associated biochemical abnormalities may mimic biliary obstruction, and thus cause diagnostic confusion. Bile duct obstructions can be classified into occlusion of the bile duct lumen, intrinsic disorders of the bile ducts, and extrinsic compression. The most common cause of biliary obstruction is duct occlusion by a stone, i.e. choledocholithiasis. Intrinsic narrowing of the bile ducts may be due to inflammatory disease like primary sclerosing cholangitis, infectious, or neoplastic biliary diseases. Extrinsic

compression of the bile ducts may result from malignancies or inflammation of the surrounding viscera.

## **2.5 Clinical features of biliary obstruction**

Biliary obstruction and hyperbilirubinemia predispose a patient to a variety of symptoms that can influence their general health status. The patient may have non-specific symptoms like pain, fatigue, nausea, anorexia and weight loss. Symptoms may also be due to duodenal obstruction associated with advanced cancer with biliary obstruction. More specific symptoms of biliary obstruction in addition to the jaundice may include patients having pale stools and dark urine as well as itching. Itching is a common and burdensome symptom in patients with cholestasis and jaundice (Song et al., 2018). The pathogenesis of itching in cholestasis is still poorly understood; it is believed that it may be mediated by specific neural pathways and pruritogenic factors including opioids, bile acids, and 5-hydroxy tryptamine. Malnutrition and cachexia are prevalent in patients with malignant biliary obstruction due to decreased nutritional intake, maldigestion, malabsorption and impaired utilization of nutrients (Padillo, Andicoberry, Pera-Madrazo, & Sitges-Serra, 2002; Bibby & Griffin, 2021). Coagulation disorders related to biliary obstruction can lead to serious bleeding disorders that have to be considered and the coagulopathy corrected with vitamin K and fresh frozen plasma (Pavlidis & Pavlidis, 2018).

Bile is normally sterile. Migration of bacteria from the small bowel into the bile ducts is normally prevented by the sphincter of Oddi. However, bacteria can invade the bile duct by ascending from the duodenum or hematogenously from the portal venous blood. The continuous flushing action of bile and the bacteriostatic effects of bile salts keeps the bile duct sterile under normal conditions, and Kupffer cells and tight junctions act to prevent translocation into the portal venous system. (Sung, Costerton, & Shaffer, 1992). Epithelium of bile ducts actively participate in the immune and inflammatory responses by secreting immunoglobulin A into the bile and using a number of innate immune reactions (Strazzabosco et al., 2018). Cholangiocytes are involved in protection of the bile duct against gut-derived pathogens and toxins, mainly by activating Toll-like receptors, nuclear receptors, and producing anti-microbial peptides (Strazzabosco et al., 2018). In acute cholangitis, these defensive mechanisms break down when biliary obstruction elevates the pressure in the bile duct, allowing the microorganisms and endotoxins in the infected bile to enter systemic circulation and induce a systemic

inflammatory response (Sung et al, 1992; Scott-Conner & Grogan, 1994; Lipsett & Pitt, 2003; Kimura et al., 2007).

Acute cholangitis is mostly due to bile duct stones in 53% to 70% of cases, malignancy in 16% to 36% of cases or biliary stent obstruction in 12% of cases (Kimura et al., 2007; Gomi et al., 2017; Lavillegrand et al., 2021). Procedures during the biliary drainage such as biliary access, dilatation and stent insertion causes damage to the bile duct epithelium and may provide a portal for bacteria entry; thus causing acute cholangitis, which is a well-known complication of biliary drainage procedures with a reported incidence rate of 0.5% to 3% after ERCP and 8% to 34% after PTBD (Li et al., 2015; ASGE Standards of Practice Committee, 2017; Chen et al., 2018; Zu et al., 2019; Sha, Dong, & Niu, 2019; Dumonceau et al., 2020). Diagnosis of acute cholangitis has traditionally been based on the clinical manifestation of acute cholangitis: fever, jaundice, and abdominal pain (Ely, Long, & Koyfman, 2018). Currently, diagnosis, severity grading, and management of cholangitis are based on the Tokyo Guidelines (Table 1–2), which were first described in 2007 (Kimura et al., 2007; Kiriyaama et al., 2013; Kiriyaama et al., 2018). Cholangitis can lead to complications such as abscess, bacteremia most commonly with gram-negative enteric pathogens, and septic syndrome (Gomi et al., 2017).

**Table 1. Tokyo Guidelines (TG18/TG13) diagnostic criteria for acute cholangitis (Modified from Kiriyaama et al., 2013; Kiriyaama et al., 2018).**

Criteria	Threshold
A. Systemic inflammation	
A-1. Fever or chills	Fever >38°C
A-2. Biological inflammatory syndrome	Leukocytes <4 10 <sup>9</sup> /L or >10 10 <sup>9</sup> /L CRP ≥10 mg/L
B. Cholestasis	
B-1. Icterus/jaundice	Total bilirubin ≥34.2 μmol/L
B-2. Abnormal liver function tests	ALP, γ-GTP, AST, ALT > 1.5 x ULN
C. Imaging	
C-1. Biliary dilatation	
C.2. Evidence of the etiology on imaging (stricture, stone, stent etc.)	
Suspected diagnosis	One item in A and one item either B or C
Definite diagnosis	One item in A, one item in B and one item in C

TG18/13: Tokyo Guidelines 2018/2013, CRP: C-reactive protein, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyltransferase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ULN: upper limit of normal.

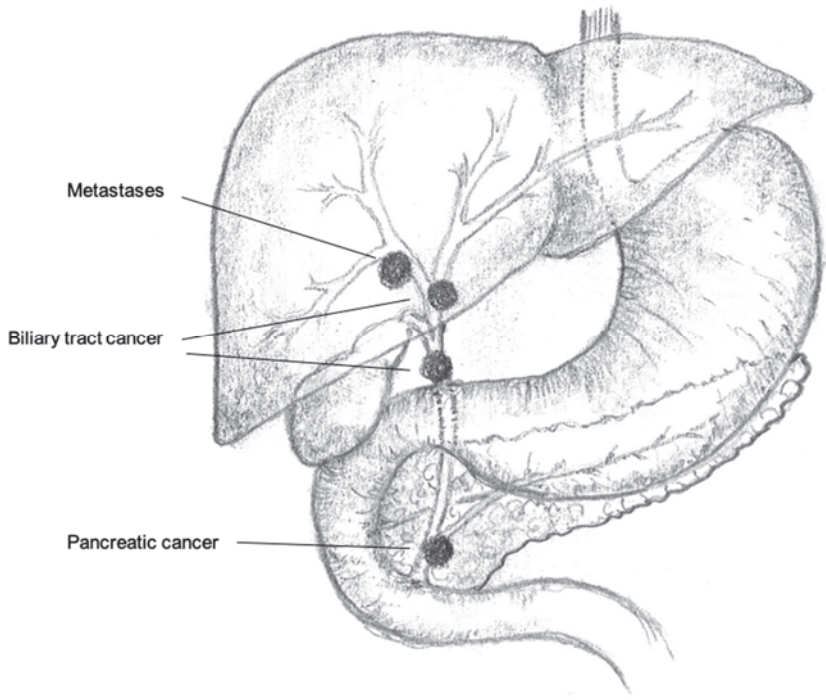
**Table 2. Tokyo Guidelines (TG18/TG13) severity assessment criteria for acute cholangitis (Modified from Kiriya et al., 2013; Kiriya et al., 2018).**

Grade	Threshold
Grade 3: severe (At least one criterium)	
Cardiovascular dysfunction	Dopamine >5 µg/kg/min or any dose of noradrenalin
Neurologic dysfunction	Consciousness disorders
Respiratory dysfunction	PaO <sub>2</sub> /FiO <sub>2</sub> ratio <300
Renal dysfunction	Oliguria or serum creatinine >176 µmol/L
Hepatic dysfunction	TT-INR >1.5
Hematological dysfunction	Thrombocytes <100 10 <sup>9</sup> /L
Grade 2: moderate (At least two criteria)	
Leukocytes	<4 10 <sup>9</sup> /L or >12 10 <sup>9</sup> /L
Fever	≥39 °C
Age	≥75 years
Hyperbilirubinemia	>85.5 µmol/L
Hypoalbuminemia	<0.7 x ILN
Grade 1: mild (No criteria grade 2 or 3)	

TG18/13: Tokyo Guidelines 2018/2013, PaO<sub>2</sub>: partial pressure of oxygen, FiO<sub>2</sub>: fraction of inspired oxygen, TT-INR: thromboplastin time international ratio, ILN: inferior limit of normal.

## 2.6 Etiology of malignant biliary obstruction

Malignant biliary obstruction (Figure 2) most commonly arises from pancreatic cancer in 42% to 58%, biliary tract cancer in 30% to 33% or metastatic gastrointestinal cancer in 18%, of which colorectal and gastric cancers are the most common (Uberoi et al., 2012; Rees et al., 2020). Table 3 shows epidemiology of the most common cancers that cause malignant biliary obstruction (Manfredi et al., 2006; Uberoi et al., 2012; Hackl et al., 2014; Riihimäki, Hemminki, Sundquist, Sundquist, & Hemminki, 2016; Engstrand et al., 2017; Rawla, Sunkara, & Gaduputi, 2019; Arnold et al., 2020; Rees et al., 2020; Valle, Kelley, Nervi, Oh, & Zhu, 2021; Finnish Cancer Registry, 2021).



**Fig. 2. Anatomical location of the most common cancers causing malignant biliary obstruction.**

**Table 3. Epidemiology of the most common cancers that causes malignant biliary obstruction.**

Cancer	Pancreatic cancer	Biliary tract cancer	Primary liver cancer	Colorectal cancer	Gastric cancer
New cases in Finland 2019 <sup>1</sup>	1083	321	521	3628 <sup>2, 3, 4, 5</sup>	598 <sup>6, 7</sup>
Incidence in Finland (x/100 000) 2019 <sup>1</sup>	19.6	5.8	9.4	65.7	10.8
ASR of incidence in Finland 2019 <sup>1</sup>	7.5	2.1	3.5	26.2	4.5
ASR of incidence in Europe 2018	7.7 <sup>8</sup>	0.3–2.0 <sup>9</sup>	4.0–6.8 <sup>10</sup>	28.8–32.1 <sup>10</sup>	4.5–11.4 <sup>10</sup>
ASR of incidence in World 2018	4.8 <sup>8</sup>	NR <sup>9</sup>	9.3 <sup>10</sup>	19.7 <sup>10</sup>	11.1 <sup>10</sup>
Etiology in malignant biliary obstruction <sup>11, 12</sup>	42–58%	30–33%	1%		18%

ASR: age-standardized rate, NR: not reported in the study, <sup>1</sup> Finnish Cancer Registry, 2021; <sup>2</sup> 25–30% develop metastases; <sup>3</sup> Engstrand et al., 2017; <sup>4</sup> Hackl et al., 2014; <sup>5</sup> Manfredi et al., 2006; <sup>6</sup> 35% develop metastases; <sup>7</sup> Riihimäki et al., 2016; <sup>8</sup> Rawla et al., 2019; <sup>9</sup> Valle et al., 2021; <sup>10</sup> Arnold et al., 2020; <sup>11</sup> Uberoi et al., 2012; <sup>12</sup> Rees et al., 2020.

### **2.6.1 Pancreatic cancer**

#### *Clinical features*

The term pancreatic cancer usually refers to ductal adenocarcinoma, which represents 85% of all pancreatic cancers (Luo et al., 2019). Intraductal papillary mucinous neoplasm represents 7% and pancreatic neuroendocrine tumor represents 5% of all pancreatic cancers. The other of subtypes, i.e. adenosquamous carcinoma, invasive mucinous cystic neoplasm, acinar cell carcinoma, squamous cell carcinoma and invasive solid pseudopapillary tumor are very rare. Many patients with early stage pancreatic cancer are asymptomatic or symptoms are mild with symptoms appearing in the late course of disease (Shires & Wilfong, 2016). The lack of early symptoms leads to a delay in diagnosis and treatment. Approximately two-thirds of pancreatic cancers are located in the head of the pancreas (71%), and the rest in the body (13%) and tail (16%) (van Erning et al., 2018). Cancers in the head of the pancreas produce symptoms usually earlier with biliary obstruction and jaundice in 38% to 75% at presentation (Payne et al., 2018; Porta et al., 2005). Tumors in the distal part of the pancreas are usually silent and symptoms appears when the disease is already advanced locally or is metastatic. Perineural invasion, a common feature of pancreatic cancer, is one of the major sources of pain related to pancreatic cancer (Wang, Chen, Li, & Zou, 2021). Pancreatic exocrine insufficiency, manifesting as steatorrhea, malabsorption and weight loss are common with a prevalence of 50% to 100% in patients with unresectable pancreatic cancer leading multifactorial syndrome known as cachexia (Bartel, Asbun, Stauffer, & Raimondo, 2015; Takeda et al., 2021). Diabetes is present in at least 50% of patients with pancreatic cancer and may predate any other manifestation of disease (Andersen et al., 2017; Salvatore, Marfella, Rizzo, & Sasso, 2015). The possibility of underlying pancreatic cancer should be taken into account especially in elderly patients without clear etiology of acute pancreatitis (Rijkers et al., 2017).

#### *Treatment*

After careful assessment, only 10 to 20% of patients with pancreatic cancer are diagnosed at an early stage and are candidates for surgical resection, while about 60% present metastatic and a poor performance status, precluding surgical

resection (Strobel, Neoptolemos, Jager, & Buchler 2019; Arrington et al., 2021). The remaining approximately 30% of pancreatic cancers are diagnosed at a locally advanced stage or as borderline resectable.

Surgical resection, in combination with systemic chemotherapy, is the only treatment that offers a potential for cure and improve survival rates for patients with pancreatic cancer (Strobel et al., 2020). Depending on the anatomical location of a tumor, pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy are the surgical options for the resection of pancreatic cancer. Surgical technique and perioperative treatment have improved in recent decades, and since then, pancreatic resections have been increasingly extended to include vascular and multi-visceral resections (Mihaljevic et al., 2021). The aim of surgical resection is to achieve radical tumor removal, i.e. R0 resection ( $\geq 1$  mm tumor-free margin), as this is associated with better survival compared to R1 ( $< 1$  mm tumor-free margin) or R2 (macroscopic tumor at the margin) resection (Strobel et al., 2019; Arrington et al., 2021).

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines of pancreatic cancer are usually used in Finland in clinical practice (Ducieux et al., 2015; ESMO Guidelines Committee, 2017; Pentheroudakis, & ESMO Guidelines Committee, 2019; European Society for Medical Oncology, 2021). The ESMO Guidelines recommend a modified regimen of 5-fluorouracil, irinotecan and oxaliplatin (mFOLFIRINOX) for adjuvant treatment after surgery in fit patients, in more frail patients a combination of gemcitabine with capecitabine or gemcitabine alone should be used. Neo-adjuvant chemotherapy before surgery with mFOLFIRINOX or a combination of gemcitabine and nab-paclitaxel has increased the proportion of surgery candidates and the outcomes of these patients has improved (Strobel et al., 2019; Muller et al., 2021; Arrington et al., 2021). The radiologic evaluation of the response after neo-adjuvant chemotherapy is difficult, and even in cases of minimal radiographic response and the potential of microscopic positive margin in a borderline resectable cancer, an aggressive surgical approach is indicated in patients with a good clinical response to achieve a survival benefit (Muller et al., 2021; Arrington et al., 2021). In advanced or metastatic stages, mFOLFIRINOX or a combination of gemcitabine and nab-paclitaxel should be considered for fit patients and monotherapy with gemcitabine for other patients.

The 5-year survival rate for patients with localized resectable disease is 35% to 45%, 10% to 15% for borderline resectable or locally advanced and less than 5% for advanced disease with distant metastases or major vascular involvement, and

median overall survival is 6.7 to 11.1 months for patients with advanced disease with chemotherapy (Park, Chawla, & O'Reilly, 2021).

### **2.6.2 Biliary tract cancer**

#### *Clinical features*

Biliary tract cancers are classified according to their anatomical primary site as follows: intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal cholangiocarcinoma and gallbladder cancer (Valle et al., 2021). The clinical presentation of symptoms of biliary tract cancer depends on the anatomical location of tumors and if there is associated metastases. Most cases of biliary tract cancer develop without any known risk factor and are sporadic. In Western countries, primary sclerosing cholangitis is the most common known risk factor, while in the East Asia parasitic infection is the most common risk factor (Khan, Tavolari, & Brandi, 2019; Valle et al., 2021). Other risk factors are biliary duct cysts and stones, cirrhosis, and hepatitis B and C viruses (Clements et al., 2020). The symptoms are usually nonspecific and the disease is often diagnosed at an advanced stage. In early stages of cancer, the patient may be completely asymptomatic, and the malignancy is identified incidentally on imaging, during the workup for elevation of liver function tests or surveillance of patients with known risk factors. Intrahepatic bile duct tumor tends to cause nonspecific symptoms of dull, aching right upper quadrant pain, cachexia, malaise, weight loss and fatigue. A tumor of the extrahepatic bile duct most often causes symptoms of biliary obstruction including jaundice, pale stools, and dark urine. Gallbladder cancer is often diagnosed incidentally during cholecystectomy but in some cases can be associated with right upper pain, biliary colic, or a tender, palpable mass. The most common clinical presentation of extrahepatic cholangiocarcinoma is jaundice in 90% of patients, while in intrahepatic cholangiocarcinoma jaundice is only seen in 10% to 15% of patients (Nakeeb et al., 1996; Forner et al., 2019).

#### *Treatment*

Patients with biliary tract cancer present usually with nonspecific symptoms, which complicates and delays diagnosis, and only 20% of patients are diagnosed at the resectable stage (Yoo et al., 2021; Valle et al., 2021).

Surgery is the only potentially curative treatment of biliary tract cancer. Radical resection is the most important prognostic factor and a microscopically negative margin is essential to achieve long-term survival (Squadroni et al., 2017; Yoo et al., 2021; Valle et al., 2021). The type and extent of resection depends on the location and size of the tumor, relationship to the anatomy of the biliary tract and adjacent vessels. Liver failure after liver resection is a significant cause of morbidity and mortality. Therefore, the assessment of future liver remnant prior to surgery is essential. The standard radical resection for perihilar cholangiocarcinoma is extended right or left hemihepatectomy, inferior parts of segment IV or V, most of the caudate lobe, hilar plate, extrahepatic bile ducts, regional lymphadenectomy and, if necessary, vascular resection. Pancreaticoduodenectomy with regional lymphadenectomy is the standard treatment for distal cholangiocarcinoma. The principle of surgical resection of gallbladder cancer depends on the stage of disease at the presentation. Most gallbladder cancers are diagnosed incidentally during or after cholecystectomy. Patients with T1a tumors can be observed without further treatment. Radical surgery for stage T1b and T2 tumors includes cholecystectomy, en bloc hepatic resection of segments IVB and V, regional lymphadenectomy and, if necessary, bile duct resection.

In Finland, ESMO Clinical Practice Guidelines for biliary tract cancer are usually used in clinical practice (Valle et al., 2016; European Society for Medical Oncology, 2021). Adjuvant treatment after surgery is used in selective case with capecitabine monotherapy as a standard in Western countries (Shroff et al., 2019). Unresectable patients are treated with a gemcitabine and cisplatin combination, which is the standard care for first line chemotherapy. This combination treatment has been associated with a significant survival advantage compared to gemcitabine alone, without substantial toxicity (Valle et al., 2010). Combination chemotherapy of 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) has recently demonstrated efficacy for second-line treatment (Sasaki, Takeda, Okamoto, Ozaka, & Sasahira, 2021). There are multiple ongoing clinical studies for adjuvant, neoadjuvant, first line and second-line chemotherapy of biliary tract cancer (Sasaki et al., 2021). Biliary tract cancer is a heterogenous group of cancers with different genetic alteration profiles. Clinically actionable alterations with matching therapeutic agents has shown promising results (Silverman et al., 2021). Also, clinical trials in phases I to III as well as several novel treatments are ongoing, assessing efficacy in advanced biliary tract cancer (Rizzo, Ricci, & Brandi, 2021). Genetic testing and precision therapeutic approaches with molecularly matched regimens have showed promising results (Okamura et al., 2021).

Patients with biliary tract cancer have a dismal prognosis, with estimated 5-year overall survival rates of 6% to 26% for localized disease and 1% to 2% for metastatic disease (Yoo et al., 2021), and median overall survival of 8.4 to 14.9 months with gemcitabine and cisplatin combination chemotherapy (Jansen et al., 2020). The 5-year survival rates range from 20% to 60% after resection in patients with biliary tract cancer (Bridgewater, Goodman, Kalyan, & Mulcahy, 2016).

### **2.6.3 Primary liver cancer**

#### *Clinical features*

Primary liver cancer can be broadly subdivided into hepatocellular cancer, typically representing 75% to 85% of all liver cancer cases, intrahepatic cholangiocarcinoma representing about 10% to 15% of cases, and other types (Arnold et al., 2020). Other types of primary liver cancer are rare including fibrolamellar hepatocellular cancer, hepatoblastoma, combined hepatocellular-cholangiocarcinoma, biliary cystadenocarcinoma, angiosarcoma, epithelioid hemangioendothelioma and undifferentiated embryonal sarcoma (Sunnawar, Katre, Policarpio-Nicolas, Katabathina, & Erian, 2016).

Hepatocellular cancer is the sixth most commonly diagnosed cancer worldwide and fourth in mortality (Chen et al., 2020). The incidence of hepatocellular cancer and the prevalence of risk factors varies worldwide (Rumgay et al., 2022). Hepatocellular cancer is closely associated with chronic inflammation and fibrosis, and 80% of hepatocellular cancer occurs in the fibrotic or cirrhotic liver (García-Pras, Fernández-Iglesias, Gracia-Sancho, & Pérez-Del-Pulgar, 2021). The incidence is highest in Asia and Africa due to high prevalence of hepatitis B virus and aflatoxin. In Europe and North America cirrhosis, caused by alcoholic or non-alcoholic fatty liver disease and hepatitis C virus are important risk factors.

The clinical presentation of hepatocellular cancer varies according to the extent of tumor and underlying liver dysfunction. Some patients may be asymptomatic when diagnosed incidentally by imaging undertaken for unrelated reasons or by surveillance imaging for chronic liver disease. Obstructive jaundice has been reported in 2.2% of patients with newly diagnosed hepatocellular cancer, but mainly due to hepatic decompensation patients may experience symptoms of worsening liver function and portal hypertension, such as ascites, encephalopathy, gastrointestinal bleeding, or jaundice (Suh, Kim, Han, & Seong, 2014). Patients

may also have chronic progressive upper abdominal pain due to tumor involvement of the sensitive liver capsule, sudden onset acute pain from tumor bleeding or rupture. In advanced stages symptoms such as cachexia, fatigue and weight loss may be present.

### *Treatment*

The aim of the treatment of patients with hepatocellular cancer is to increase survival while maintaining the highest possible quality of life. Selection of appropriate treatment should be evaluated individually in multidisciplinary teams based on the assessment of tumor extent, liver function, patients' comorbidities and performance status. The Barcelona Clinic Liver Cancer (BCLC) system has been a widely used staging system and treatment strategy for hepatocellular cancer (Reig et al., 2022). Surgical resection, liver transplantation, tumor ablation (radiofrequency or microwave ablation), transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT) and tyrosine-kinase inhibitors are the treatments with a proven survival benefit for hepatocellular cancer (Forner, Reig, & Bruix, 2018; Vogel et al., 2018; Chen et al., 2020).

Hepatic resection is the treatment of choice for hepatocellular cancer in patients without cirrhosis, while patients with cirrhosis should be carefully evaluated to avoid complications related to treatment and to achieve long-term survival (Forner et al., 2018). Patients with a single tumor and preserved liver function are the best candidates for liver resection. The liver resection requires a detailed assessment of liver function and future liver remnant volume prior to surgery to avoid postoperative liver failure. Liver transplantation offers the possibility to cure both the tumor and the underlying cirrhosis (Forner et al., 2018; Vogel et al., 2018). The Milan criteria, i.e. a single nodule  $\leq 5$ cm or up to 3 nodules  $\leq 3$ cm, are the benchmark and widely used criteria for transplantation for patients with hepatocellular cancer (Mazzaferro et al., 1996; Forner et al., 2018). Tumor ablation is a widely accepted therapy for the treatment of small tumors and cases of unresectable tumors for patients with early stage hepatocellular cancer (Forner et al., 2018; Vogel et al., 2018; Chen et al., 2020). TACE or SIRT are effective treatments in patients with intermediate stage hepatocellular cancer (Forner et al., 2018; Vogel et al., 2018; Chen et al., 2020).

Recent systemic therapy includes tyrosine kinase inhibitors, vascular growth factor inhibitors and the combination of immunotherapy with vascular growth factor inhibitor that are used for the treatment of patients with advanced or

metastatic disease with a proven survival benefit (Llovet et al., 2008; Bruix et al., 2017; Kudo et al., 2018; Abou-Alfa et al., 2018; Zhu et al., 2019; Finn et al., 2020; Chen et al., 2020). Immunotherapy with combinations of several tyrosine kinase drugs is ongoing as well as adjuvant treatment after surgery (Llovet et al., 2021).

The prognosis of patients with hepatocellular cancer and obstructive jaundice is poor with a median survival of four months (Suh et al., 2014).

## **2.6.4 Colorectal cancer**

### *Clinical features*

Population-based studies have shown that around 25% to 30% of patients diagnosed with colorectal cancer develop liver metastases during the course of their disease (Manfredi et al., 2006; Hackl et al., 2014; Engstrand et al., 2017) and at the time of diagnosis of metastatic disease the most common site is the liver in 68% to 75% of patients (Wang et al., 2020). Malignant biliary obstruction has been reported to occur in 10% of patients with known metastatic colorectal cancer, however, most often fairly late in the course of disease (Nichols et al., 2014).

### *Treatment*

There are several guidelines in the Western world to provide a series of evidence-based recommendations to assist in the treatment of patients with metastatic colorectal cancer; for example, ESMO and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines (Van Cutsem et al., 2016; Benson et al., 2021). ESMO Clinical Practice Guidelines of metastatic colorectal cancer are usually used in Finland in clinical practice (Van Cutsem et al., 2016; European Society for Medical Oncology, 2021). The treatment of patients with colorectal cancer in Finland is based on the Finnish national recommendation for the treatment of colorectal cancer (HUS FICAN Southin nimeämä hoitosuositusryhmä, 2019).

The treatment strategy should be focused on complete resection of liver metastases whenever possible with a perioperative chemotherapy option. Surgical resection represents the only potentially curative approach to colorectal liver metastases (Hackl et al., 2014). Only 25% of patients with colorectal liver metastases qualify for resection at initial presentation, however, down-staging

using chemotherapy has increased resection rates to 30% to 45% (Lam et al., 2012; Hackl et al., 2014). Currently, there is no limit to how many metastases can be resected providing that clear margins are achieved, ability to preserve adequate future liver remnant, adequate vascular inflow and outflow as well as biliary outflow (Martin et al., 2020; Cassar, Geoghegan, & Hoti, 2022). Liver resection with a wide resection margin (>10mm) should be attempted whenever possible. However, liver resection should not be precluded if narrower margins are anticipated when resection borders are limited due to vascular or biliary structures, since R1 (<1mm) margins improve survival (Martin et al., 2020; Andreou et al., 2021; Cassar et al., 2022). Evaluation of future liver volume and estimation of the functional capacity of the liver should be performed prior to surgery to avoid liver failure. Resection can be performed openly or laparoscopically, synchronized with colorectal surgery or either before or after colorectal surgery. Local ablative therapies are suitable for selected patients with small liver metastases (<3cm), located deep in the liver parenchyma, and patients with co-morbidities and unfit for major liver resection (Xu, Tang, Jin, & Dai, 2018; Di Martino et al., 2020).

Chemotherapy is based on fluoropyrimidine, irinotecan and oxaliplatin such as FOLFOX and combination of 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) (Yu & Cheung, 2018). The combination of local ablative therapy and chemotherapy, as well as new targeted therapies against epidermal growth factor receptor and vascular endothelial growth factor are the standard treatments in patients with non-resectable metastases (Hu, Lan, Huang, Li, & Jin, 2021). Colorectal cancer has tremendous capacity for somatic mutations with high heterogeneity (Kim & Bodmer, 2022). Tumor gene status with KRAS/NRAS and BRAF mutations and microsatellite instability (MSI) status are recommended as prognostic and predictive markers to determining response to treatment (Benson et al., 2021). The chromosomal instability pathway accounts for approximately 70% of colorectal cancers and is characterized by alteration of the number and structure of chromosomes and accumulated mutations in oncogenes and tumor suppressor genes. The MSI is observed in approximately 10% to 20% of colorectal cancers characterized by defect in the genes of mismatch repair systems. The patients with high deficient mismatch/microsatellite instability (MSI-high) have a 15% higher survival rate than patients with MSI-low (Kang et al., 2018), and being treated with immunotherapy as a standard (André et al., 2020; Fan et al., 2021).

In a Finnish nationwide study of colorectal cancer and liver metastases 5-year overall survival rates after diagnosis of metastatic colorectal cancer were 66% for patients with R0–1 resection, 40% for patients with R2 resection or ablation, 6%

for patients with systemic therapy and 0% with best supportive care (Osterlund et al., 2021). Of note, the patients with single colorectal cancer liver metastasis after resection have a long-term survival similar to colorectal cancer patients without any metastases (Hackl et al., 2014).

Patients with metastatic colorectal cancer and malignant biliary obstruction and jaundice have a poor prognosis with a median survival of about one month when treated with supportive care (Walia et al., 2008). After successful biliary drainage survival is still poor with a median survival of less than two months, but nine months of survival benefit is achieved in patients who were able to receive subsequent chemotherapy (Nichols et al., 2014; Sellier et al., 2017).

### **2.6.5 Gastric cancer**

#### *Clinical features*

A Swedish nationwide registry study has shown that about 35% of patients with gastric cancer develop metastases and most commonly in the liver (Riihimäki et al., 2016). The incidence of malignant biliary obstruction in patients with metastatic gastric cancer has been reported to range from 1.3% to 2.3% (Papachristou & Fortner, 1978; Migita, Watanabe, Yoshioka, Kinoshita, & Ohyama, 2009; Gwon et al., 2012).

#### *Treatment*

Surgical resection is still the cornerstone of gastric cancer treatment with curative intent, especially at early stages. The choice of surgical procedure depends on the tumor, the clinical stage, and the histologic type. Total gastrectomy is usually performed for tumors in the upper third of the stomach, while distal gastrectomy appears to be sufficient for tumors in the lower two-thirds of the stomach (Smyth et al., 2016; Smyth, Nilsson, Grabsch, van Grieken; & Lordick, 2020). Large tumors in the middle of the stomach or infiltrative disease, e.g. linitis plastica, require total gastrectomy. Lymphadenectomy with D2 dissection is recommended for patients who are undergoing potentially curative resection. Potential survival benefit of surgical resection may be achievable with a carefully selected subset of patients with metastases of gastric cancer in the liver only (Granieri et al., 2021).

In a large proportion of gastric cancer patients, the disease has been shown to recur after primary resection, and therefore, multimodality therapy including surgery, adjuvant or neo-adjuvant chemotherapy (docetaxel, oxaliplatin/cisplatin, 5-fluorouracil/capecitabine) or adjuvant chemoradiotherapy are standard treatments for non-metastatic disease (Smyth et al., 2016; European Society for Medical Oncology, 2021). Physically fit patients with inoperable locally advanced and metastatic gastric cancer are treated with the abovementioned systemic chemotherapy with improved survival compared to best supportive care alone (Wagner et al., 2017), and an anti-HER2 drug combination and immunotherapy have been used for a rare subset of patients (Denlinger, Matkowskyj, & Mulcahy, 2021).

Patients with early stage gastric cancer have a distinctly excellent outcome after resection with a disease-specific 5-year survival of 90% (Gold et al., 2013). In a Finnish nationwide population-based study of gastric cancer, 31% of the patients had advanced cancer and 5-year overall survival rate of the cohort was 34.6%. (Kauppila et al., 2020). In a Swedish registry study, patients with metastatic gastric cancer had a poor prognosis with a median survival of six months in patients younger than 60 years compared to older patients with a survival of three months, and in patients with liver metastases two months (Riihimäki et al., 2016). After biliary drainage of malignant biliary obstruction, the survival of patients with gastric cancer is poor with a median survival of two months, but six months of survival benefit is achieved with subsequent chemotherapy (Migita et al., 2009).

## **2.7 Imaging of malignant biliary obstruction**

Transabdominal ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive imaging modalities that are used to determine the etiology of jaundice (Hindman et al., 2019). US is typically the initial imaging modality for abdominal pain and suspected obstructive jaundice. US has been shown to be accurate for detecting extrahepatic biliary obstruction, with a reported accuracy range from 78% to 98%; however, the cause of the obstruction is less often definitely seen on US, with reported accuracies ranging from 23% to 88% (Tse et al., 2006). CT and MRI are highly accurate for detecting malignant biliary obstruction and for staging of pancreatic and biliary malignancies with accuracies varying from 80.5% to 97% (Hindman et al., 2019). CT and MRI provide cross-sectional anatomical imaging of all the organs of the abdomen and staging includes important information on tumor extensions, involvement of the

biliary tract and confluence, vascular encasement, regional adenopathy, liver and distant metastases. Multiphase contrast-enhanced multidetector-computed tomography (MD-CT) is a standard imaging technique for a patients with malignant biliary obstruction for staging the malignancy and determination of treatment options (Ducreux et al., 2015; Valle et al., 2021). MRI and the magnetic resonance cholangiopancreatography (MRCP) method provide detailed anatomical depictions of the biliary tract (Hyodo et al., 2012). MRI has been shown to be more sensitive than CT for the detection of liver metastases (Alabousi et al., 2021; Tsili, Alexiou, Naka, & Argyropoulou, 2021). Moreover, MRI is useful for detection of small, i.e. < 10 mm liver lesions, for which there are limitations in the characterization by CT (Vreugdenburg et al., 2016; Lincke & Zech, 2017). Positron emission tomography-computed tomography (PET-CT) can provide additional value for patients with undetermined etiology of biliary obstruction or when recurrence is suspected with negative CT findings, but is not considered as the primary or conventional method (Wang et al., 2015; Daamen et al., 2018). Endoscopic ultrasound (EUS) is largely used in the staging and its great advantage is the ability to provide tissue samples for the confirmation of diagnosis before chemotherapy or chemoradiation (Hindman et al., 2019). ERCP and PTBD currently have more of a therapeutic than diagnostic role in biliary obstruction.

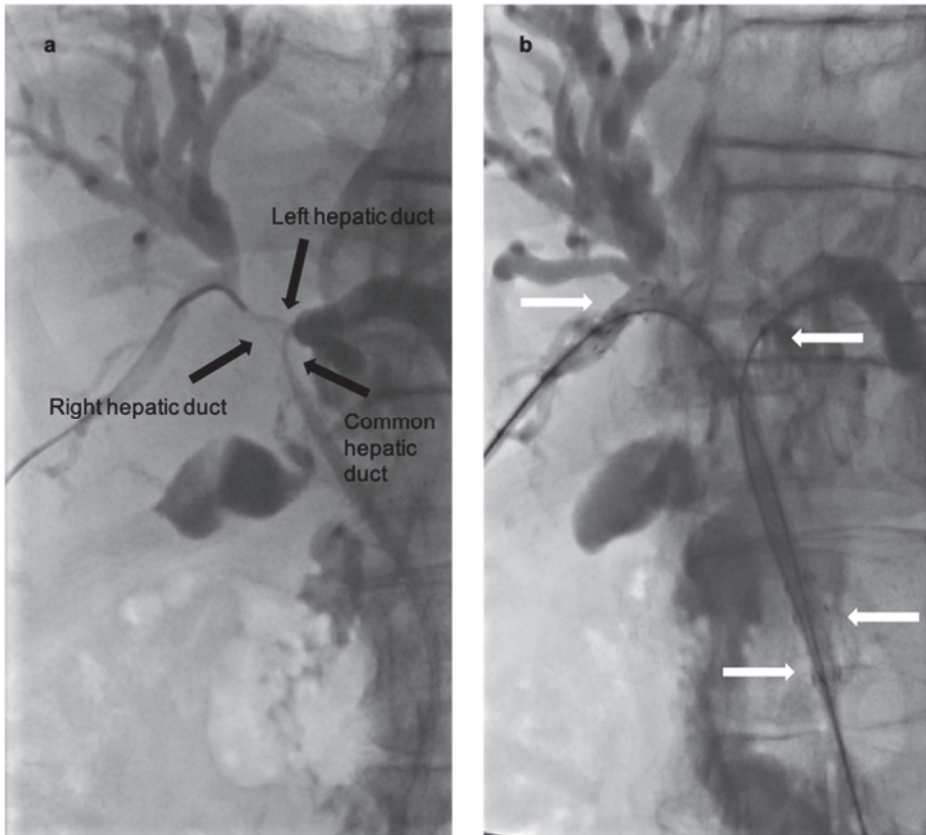
## **2.8 Biliary drainage techniques**

ERCP with biliary drainage of the malignant biliary obstruction is a minimally invasive method and the primary treatment choice worldwide. However, PTBD (Figure 3) is often a suitable treatment option when ERCP is not feasible due to duodenal obstruction or previous surgery, such as Roux-en-Y anastomosis that has altered the anatomy, or when endoscopic drainage has been insufficient or failed due to invisible or inaccessible duodenal papilla. Moreover, PTBD appears to be superior for palliation compared to endoscopic drainage for the treatment of patients with advanced unresectable hilar malignancies with biliary obstruction (Moole et al., 2016). PTBD is an invasive procedure with a risk of complications such as bleeding, bile leakage, cholangitis and sepsis, with reported complication rates varying from 6% to 30% in series (Tapping et al., 2011; Uberoi et al., 2012; Rees et al., 2020). Antibiotic prophylaxis is recommended to patients undergoing PTBD for prevention of cholangitis (Sutcliffe et al., 2015). EUS-BD has become a promising alternative to PTBD in biliary drainage following failed ERCP (Pawa, Pleasant, Tom, & Pawa, 2021). The available evidence is based on a recent

systematic review and network meta-analysis showed that differences between ERCP, EUS-BD and PTBD were likely small and did not favor any procedures for drainage of malignant biliary obstruction; however, ERCP with or without EUS should be considered as the preferred modality for drainage because these procedures allow simultaneous tissue acquisition to confirm the diagnosis (Xie et al., 2022). The role of surgical biliary bypass has diminished in recent decades with the development of abovementioned non-operative interventions. However, if non-resectable disease is found during operation, biliary bypass should be considered for patients with low surgical risk, good performance status, and patients who are projected to have reasonable survival rates (Bliss et al., 2016; Ciambella, Beard, & Miner 2018). The aim of the biliary drainage is to relieve symptoms and improve quality of life and also enable chemotherapy treatment by reducing high bilirubin level (Robson et al., 2010; Barkay et al., 2013; Levy et al., 2016).

## **2.9 Outcome of the patients with malignant biliary obstruction treated with PTBD**

Patients with malignant biliary obstruction usually have a poor prognosis due to their advanced disease. Studies concerning the survival of patients with malignant biliary obstruction after PTBD are very heterogenous in terms of various temporality, epidemiological and clinical data included. In these studies, the reported median overall survival has been about two to six months after PTBD (Saluja et al., 2008; Hong et al., 2013). Park et al. (2009) reported a median survival of three months for patients with advanced unresectable biliary tract cancer without biliary drainage, chemotherapy, or radiotherapy. The reported 30-days mortality after PTBD varies considerably in the literature from 2% to 41% (van Delden & Lameris, 2008; Coelen et al., 2018); however, in large cohort studies, the 30-day mortality rates were 19.8% to 23.1% after PTBD for patients with unresectable malignant biliary obstruction (Uberoi et al., 2012; Rees et al., 2020). Early mortality after PTBD is largely due to underlying malignant disease (van Delden & Lameris, 2008). The literature has reported 2% to 8% 30-day mortality related to the PTBD procedure (Tapping, et al 2011; Turan et al., 2021).



**Fig. 3. Percutaneous biliary drainage (PTBD). a). Cholangiography from right and left hepatic ducts demonstrates hilar cholangiocarcinoma (black arrows). b). Self-expanding metal stents (SEMS) are placed across the hilar bile duct obstruction (white arrows).**

### **2.10 Cholangitis and outcome in patients with malignant biliary obstruction**

The survival of the patients with malignant biliary obstruction treated with PTBD has varied from 2.0 to 5.4 months in earlier studies (Table 4) in which cholangitis has been defined (Lee et al., 2007; Saluja et al., 2008; Ahn, Lee, Lim, & Lee, 2013; Li et al., 2015; Sha et al., 2019; Zu et al., 2019; Rees et al., 2020). However, in these studies the impact of cholangitis on survival has not been systematically

**Table 4. Summary of studies concerning cholangitis and survival in patients with malignant biliary obstruction after percutaneous transhepatic biliary drainage (PTBD).**

Study, year	Cancer	n	Cholangitis before PTBD, n (%)	Cholangitis after PTBD, n (%)	30-day mortality, n (%)	1-year survival, n (%)	Median overall survival months (95% CI)
Lee et al., 2007	BTC	100		19 (19.0)	2 (2)	NR	NR
Saluja et al., 2008	GBC	27		3 (11.1)	1 (3.7)	NR	2.0 (NR)
Ahn et al., 2013	PC, BTC, HCC, DC, mC	409		106 (25.9)	16 (3.9)	NR	NR
Li et al., 2015	PC, BTC, LC, mC	159	18 (11.3)	25 (36.1)	NR	NR	4.2 (NR)
Sha et al., 2019	PC, BTC, LC, mC	155	13 (8.4)	56 (36.1)	26 (16.8)	NR	NR
Zu et al., 2019	BTC, PC, mC	104		19 (18.3)	NR	NR	5.4 (NR)
Rees et al., 2020	PC, BTC, LC, mC	16 822		656 (3.9)	3885 (23.1)	NR	3.1 (NR)

PTBD: percutaneous transhepatic biliary drainage, BTC: biliary tract cancer, GBC: gallbladder cancer, PC: pancreatic cancer, HCC: hepatocellular cancer, DC: duodenal cancer, mC: metastatic cancer, LC: liver cancer, NR: not reported in the study.

analyzed and the focus has mainly been on the technical aspects of biliary drainage, complications and 30-day mortality.

Furthermore, many of the other previous studies have been focused on preoperative biliary drainage before surgery, complications and cholangitis and their effect on postoperative morbidity, mortality and outcome in patients with resectable malignant biliary obstruction. Biliary drainage is an invasive procedure with a risk of complications, and cholangitis has been found to be a prognostic factor for shorter outcome in patients with resectable cancer with malignant biliary obstruction (Kurahara et al., 2016; Akita et al., 2017). Based on current evidence, preoperative biliary drainage is not routinely recommended, but it may be useful in patients with symptoms such as cholangitis, malnutrition, and long-lasting jaundice (Moole, Bechtold, & Puli, 2016; Lee et al., 2018; Mehrabi et al., 2020).

## 2.11 Chemotherapy and outcome in patients with malignant biliary obstruction and hyperbilirubinemia

Performance scales (Table 5) are used to assess patient eligibility of patient for clinical trials, in daily clinics to predict whether a patient can tolerate and respond to cancer therapy, and assess eligibility for services such as home care. In randomized clinical trials representing mainly patients with good performance status, i.e. Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1 (96.4%) and exceedingly few patients with poor performance status (ECOG PS  $\geq 2$ , 3.6%), severely limit the generalizability of trial results for clinical practice (Abi Jaoude et al., 2020; Eastern Cooperative Oncology Group, 2022).

**Table 5. ECOG performance status (Modified from Eastern Cooperative Oncology Group, 2022).**

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

ECOG PS: Eastern Cooperative Oncology Group performance status.

In daily clinical practice, chemotherapy is usually considered for patients with bilirubin levels lower than 1.5-fold of the upper limit of normal (ULN) and ECOG PS 0–2 (Valle et al., 2010; Conroy et al., 2011). Oncological treatment is challenging due to hyperbilirubinemia in patients with malignant biliary obstruction (Lamarca et al., 2015; Jansen et al., 2020). A high bilirubin level can diminish hepatic clearance and alter drug metabolism, increasing toxicity; therefore, high bilirubin levels have been considered an exclusion criterion for chemotherapy and these patients have typically been excluded from clinical studies (Field & Michael, 2008; Valle et al., 2010; Conroy et al., 2011; Vogel et al., 2015). Limited knowledge is available regarding appropriate chemotherapy dosing and management in patients with higher bilirubin levels. New chemotherapy combinations have shown a positive trend of prolonged survival in patients with pancreatic and biliary tract cancer (Valle et al., 2010; Conroy et al., 2011; Kieler et al., 2020; Rizzo et al., 2020; Rizzo & Brandi, 2021).

Despite the increasing diagnosis of malignancies in the elderly, this group of patients are underrepresented in cancer research and clinical trials; less than 20% of the patients included were over 64 years old and less than 10% over 74 years old (Hurria et al., 2014; Lopez-Lopez et al., 2020).

There are very limited data concerning the utility of chemotherapy for patients with malignant biliary obstruction not suitable for endoscopic biliary drainage and therefore treated with PTBD (Migita et al., 2009; Kasuga et al., 2012; Gwon et al., 2012; Crosara Teixeira et al., 2013; Hong et al., 2013; Li et al., 2015; Vandenabeele, Dhondt, Geboes, & Defreyne, 2017; Dhondt et al., 2020). Table 6 summarizes the results of studies and shows survival among patients with or without chemotherapy after PTBD. The etiology of biliary obstruction has varied in previous studies and in all but three of these studies (Migita et al., 2009; Kasuga et al., 2012; Dhondt et al., 2020), information concerning chemotherapy was brief, with few or no details about the regimens, and the focus has mainly been on the technical aspects of biliary drainage.

## **2.12 Best supportive care**

There is wide variability in the use of the terms “supportive care” and “best supportive care” in NCCN Guidelines. “Supportive care” is mostly limited to describing the management of cancer-related complications and adverse effects of treatment and “best supportive care” describes management of patients without active cancer treatment with drugs (Mo, Urbauer, Bruera, & Hui, 2021). A

consensus published in 2012 presented a tool to define best supportive care into four domains: multidisciplinary care, documentation, symptom assessment, and symptom management in clinical trials with patients who have advanced cancer (Zafar et al., 2012). However, in most clinical trials best supportive care with objectives, treatments and methods was not defined and thus studies often failed to standardize best supportive care across trial sites, as well as evidence-based symptom management (Sanz Rubiales, Sanchez-Gutierrez, Flores Perez, & del Valle Rivero, 2020; Nipp et al., 2015). These problems with trial design threaten validity and may result in biased outcomes and potentially flawed conclusions (Nipp et al., 2015).

Patients often need comprehensive physical, psychological, social, mental support and rehabilitation at any stage of disease. Together with anticancer therapies, supportive and palliative interventions should be integrated in a patient-centered manner at all stages of disease (Jordan et al., 2018).

**Table 6. Summary of studies comparing survival among patients with or without chemotherapy after percutaneous transhepatic biliary drainage (PTBD).**

Study, year	Cancer	With subsequent chemotherapy		Without subsequent chemotherapy		Overall	
		n (%)	Months (95% CI)	n (%)	Months (95% CI)	n	Months (95% CI)
Migita et al., 2009	mGC	17 (44.7)	8.6 (NR)	21 (55.3)	2.0 (NR)	38	2.6 (NR)
Kasuga et al., 2012	mCRC, mGC	39 (52.7)	9.1 (NR)	35 (47.3)	2.2 (NR)	74	3.2 (NR)
Gwon et al., 2012	mGC	60 (51.3)	5.7 (3.7–7.8)	57 (48.7)	1.8 (1.2–2.5)	117	3.5 (2.8–4.1)
Crosara Teixeira et al., 2013	BTC, mGC, PC, mCRC, other	33 (46.5)	13.7 (NR)	38 (53.5)	1.2 (NR)	71	2.9 (0.6–5.2)
Hong et al., 2013	mGC	NR	NR	NR	NR	50	6.0 (0.5–11.4)
Li et al., 2015	BTC	23 (14.5)	10.4 (NR)	136 (85.5)	3.7 (NR)	159	4.2 (NR)
Vandenabeele et al., 2017	BTC, PC, mCRC, mGC, mEC, other	28 (30.4)	5.7 (3.0–8.4)	63 (68.5)	1.1 (0.8–1.4)	92	1.6 (1.2–2.0)
Dhondt et al., 2020	BTC, PC, mCRC, mGC, mOC, other	45 (37.8)	6.9 (NR)	74 (62.2)	1.6 (NR)	119	NR

CI: confidence interval, mGC: metastatic gastric cancer, mCRC: metastatic colorectal cancer, BTC: biliary tract cancer, PC: pancreatic cancer, mEC: metastatic esophageal cancer; mOC: metastatic ovarian cancer, NR: not reported in the study.



### **3 Aims of the study**

The aims of the present study were as follows:

1. To evaluate the survival and predictive factors for survival of patients with malignant biliary obstruction treated with PTBD.
2. To evaluate the impact of cholangitis on survival in patients with gastrointestinal cancer and malignant biliary obstruction treated with PTBD.
3. To evaluate the survival benefit of chemotherapy compared to best supportive care after PTBD for patients with pancreatic or biliary tract cancer with malignant biliary obstruction.



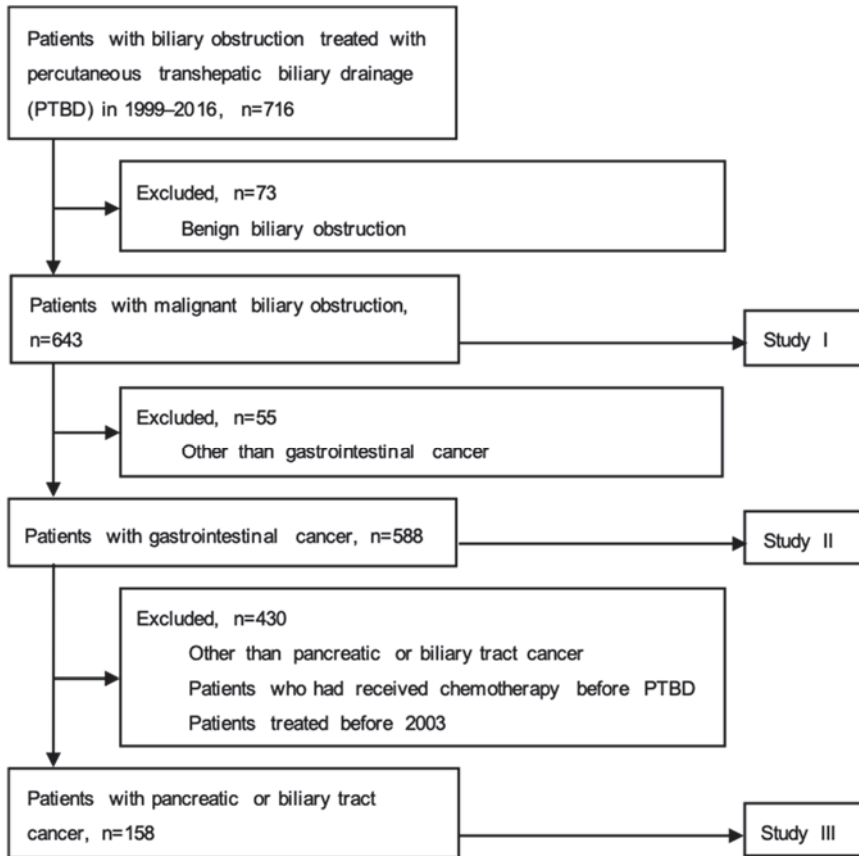
## 4 Material and methods

### 4.1 Patients

This study consists of patients who were treated with PTBD for biliary obstruction between 1999 and 2016 at the Oulu University Hospital. ERCP is the primary treatment for the drainage of biliary obstruction at our unit. PTBD was done if ERCP was not feasible due to duodenal obstruction or previous surgery that has altered patient anatomy, or when endoscopic drainage has been insufficient or failed. Patient data have been collected from a radiological planning program according to the procedure codes. All patients who had a malignant biliary obstruction and were treated with PTBD were retrospectively retrieved for the analysis of the study. Patients who had a benign biliary obstruction were excluded in the present study. A flowchart of study population selection is shown in Figure 4.

PTBD procedures were performed under anesthesia by an experienced interventional radiologists using previously documented methods, guided by ultrasonography and fluoroscopy (Sutter & Ryu, 2015).

The following data were retrieved from electronic medical records: age, gender, pre-procedure American Society of Anesthesiologists physical status classification (ASA class) (American Society of Anesthesiologists, 2022), ECOG PS (Eastern Cooperative Oncology Group, 2022), comorbidities, cancer type, obstruction level, and laboratory values. The laboratory values were obtained within 7 days before PTBD and 30 days after PTBD; in addition, within 7 days after the diagnosis of cholangitis. The following laboratory values were analyzed: hemoglobin, leukocytes, thrombocytes, C-reactive protein (CRP), thromboplastin time international ratio (TT-INR), creatinine, albumin, bilirubin, alanine aminotransferase, and gamma-glutamyltransferase. The blood culture and bile culture results after biliary drainage were also collected. Cancers were classified according to cancer type and whether they were primary or metastatic. The level of biliary obstruction was defined as upper (hilum), middle (common hepatic duct), or lower (common bile duct). Time of death was acquired from death certificates (Statistics Finland, 2022). Approval for the study was obtained from Oulu University Hospital (No.140/2011).



**Fig. 4. Flowchart of study population selection.**

## **4.2 Methods**

### **4.2.1 Study I**

Study I comprised all 643 patients who were treated with PTBD for malignant biliary obstruction between 1999 and 2016.

The study was conducted to evaluate the survival following PTBD in patients with malignant biliary obstruction and to evaluate predictive factors for survival. Survival rates were defined as the interval between initial PTBD and patient's death or last follow-up.

### **4.2.2 Study II**

The study includes all 588 consecutive patients with gastrointestinal cancer and malignant biliary obstruction treated with PTBD between 1999 and 2016.

The patient population was divided into three groups: patients with cholangitis onset before drainage, patients with cholangitis onset after drainage, and patients without cholangitis. The diagnosis and severity of cholangitis was determined according to the Tokyo Guidelines 2013 and the severity was graded as mild, moderate, or severe (Kiriyama et al., 2013). Criteria are described in more detail in Tables 1 and 2. Laboratory tests were taken within 48 hours of the diagnosis were used to assess severity of cholangitis according to the Tokyo Guidelines.

Study II was conducted to evaluate whether cholangitis has any effect on survival in gastrointestinal cancer patients with malignant biliary obstruction treated with PTBD, and whether survival differs in patients with cholangitis before PTBD and those who develop cholangitis after PTBD. We were also interested in the survival of patients who received chemotherapy after successful biliary drainage.

Survival was defined as the interval from PTBD to the patient's death or last follow-up. The survival time for patients who received chemotherapy was defined as from the initiation of chemotherapy to the patient's death or last follow-up.

### **4.2.3 Study III**

Study III included 158 patients with chemotherapy-naïve pancreatic or biliary tract cancer with malignant biliary obstruction who were treated with PTBD and

followed at the Oulu University Hospital between 2003 and 2016. The patients who have undergone radical surgery for cancer after PTBD were excluded in the study.

The study investigated the benefit of chemotherapy compared to best supportive care after PTBD in patients with pancreatic or biliary tract cancer with hyperbilirubinemia caused by biliary obstruction. The patient population was divided into two groups: patients eligible to receive chemotherapy, and patients with only best supportive care after PTBD. Survival was defined as the interval starting from the PTBD in the group of best supportive care or the initiation of chemotherapy in the chemotherapy group and ending with the patient's death or last follow-up.

### **4.3 Statistical analysis**

Summary data were presented as means with standard deviations (SDs) or as medians with 25th–75th percentiles (interquartile range; IQR). The continuous variable, bilirubin concentration, was categorized using a receiver-operating characteristic curve (ROC-curve) analysis for mortality with a sensitivity of approximately 80% and a Youden's index of 1.30, giving a cut-off value of 60.0  $\mu\text{mol/L}$  (Study I). Between-group comparisons for continuous data were performed using analysis of variance (ANOVA) (>2 groups) and Student's t-test or Welch's t-test when comparing two groups (the latter if the assumption of homoscedastic variances did not hold). Pearson's  $\chi^2$  test or Fisher's exact test were used for categorical data. The log-rank test was used to compare survival data in univariate analyses. In study I, a multivariable Cox proportional hazards model was used to identify possible risk factors for 1-year mortality, with results presented as hazard ratio (HR) and 95% confidence interval (CI). The study period was divided into three six-year periods to adjust for the possible impact of study period and adjusted HR's are presented. In study II and III, to minimize biases and validate patient groups in the multivariable model, a directed acyclic graph (DAG) was constructed to derive a minimally sufficient adjustment set. The DAG was drawn using the DAGitty tool (Textor, van der Zander, Gilthorpe, Liskiewicz, & Ellison, 2016). In study II, the DAG model indicated that the following parameters should be taken into account in the Cox model: number of co-morbidities (none, 1–2, >2), ASA class (1–2, 3, 4), type of cancer (pancreatic, biliary tract, metastatic gastrointestinal), the level of the biliary obstruction (upper, middle, lower), bleeding, and other complications. A multivariable adjusted Cox proportional hazards model was used in study II to determine the impact of cholangitis on 30-

day and 1-year mortality. In study III, the DAG model indicated that the following parameters should be taken into account in the adjusted Cox model: patient age ( $\leq 70$  or  $> 70$  years), number of co-morbidities (none, 1–2,  $> 2$ ), ECOG PS (0–1, 2, 3–4), bilirubin level after drainage ( $< 60$  or  $\geq 60$   $\mu\text{mol/L}$ ; according to a receiver-operating characteristic curve from study I), and the type of cancer (pancreatic or biliary tract). In study III, survival in the chemotherapy group was defined from the initiation of chemotherapy and a multivariable adjusted time-dependent Cox proportional hazard model was used to avoid and minimize the immortal time bias, i.e. the time between diagnosis and the initiation of cancer treatment, to determine the impact of chemotherapy treatment on the 1-year mortality (Agarwal et al., 2018). The results of the Cox model were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Two-tailed p-values were reported and p-values  $< 0.05$  were considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows, Version 21.0 (Study I), Version 25.0 (Study II and III), (IBM Corp, Armonk, NY).



## 5 Results

The studies with included patients and the main results of the study are shown in Table 7.

**Table 7. Studies and main results of the study.**

Study	Patients included in study	Main result
I	The study group comprised 643 patients with malignant biliary obstruction treated with PTBD.	The median overall survival after drainage was 2.6 months. Cox regression model revealed that shorter survival time was associated with metastatic cancer, ECOG PS $\geq 2$ , ASA class 4, and bilirubin level after PTBD $\geq 60.0$ $\mu\text{mol/L}$ .
II	The study group comprised 588 patients with malignant biliary obstruction treated with PTBD, of which 258 patients had pancreatic cancer, 222 had biliary tract cancer, and 108 had metastasis from cancers of the gastrointestinal tract, of which 52 (48.1%) had gastric cancer and 43 (39.8%) had colorectal cancer.	The median survival was 1.8 months among 156 patients with cholangitis before PTBD, 3.0 months among 215 patients with cholangitis after PTBD, and 3.2 months among 217 patients without cholangitis. The HR for 1-year mortality for patients with cholangitis before PTBD was 1.3 (95% CI 1.06–1.67; $p=0.015$ ) compared to the patients with cholangitis after PTBD. The median survival of the chemotherapy-treated patients was 5.2 months for 10 patients with cholangitis before PTBD, 9.4 months for 24 patients with cholangitis after PTBD and 15.3 months for 20 patients without cholangitis.
III	The study group comprised 158 patients with malignant biliary obstruction treated with PTBD, of which 82 had pancreatic cancer and 76 had biliary tract cancer.	The median survival of the 32 chemotherapy-treated patients was 11.7 months, while 126 patients treated with best supportive care had a survival of 1.7 months. The HR for 1-year mortality was 0.22 (95% CI 0.12–0.41; $p<0.001$ ) for patients who received chemotherapy.

ECOG PS: Eastern Cooperative Oncology Group performance status, ASA class: American Society of Anesthesiologists physical status classification, PTBD: percutaneous transhepatic biliary drainage, HR: hazard ratio, CI: confidence interval.

## 5.1 Study I

The study group comprised 643 patients with malignant biliary obstruction. A SEMS was inserted in 498 patients (77.4%), a plastic stent with combined ERCP procedure was used in 21 patients (3.3%), and external drainage was used in 124 patients (19.3%). The reasons for PTBD were as follows: Roux-en-Y reconstruction (n=63, 9.8%), duodenal obstruction (n=140, 21.8%), failed ERCP drainage (n=213, 33.1%), insufficient ERCP drainage (n=105, 16.3%), biliary obstruction in the hilum (n=74, 11.5%) and other reasons (n=48, 7.5%). After PTBD, surgery was carried out for 38 patients (5.9%); of which resection of cancer was performed for 15 patients (2.3%), biliary bypass for 9 patients (1.4%) and explorative laparotomy for 14 patients (2.2%).

Patient demographics and clinical characteristics are presented in Table 8. The mean patient age was 69.3 years (range 26–93 years). Bile duct obstruction was due to primary cancer in 480 patients (74.7%); of which 246 patients had pancreatic cancer (51.2%) and 210 patients had biliary tract cancer (43.8%). Bile duct obstruction was due to metastases in 163 patients (25.3%); among the metastases, the most common primary cancers were gastric cancer in 52 patients (31.9%) and colorectal cancer in 43 patients (26.4%). The obstruction was in the upper third of the bile duct in 272 patients (42.3%), in the middle third in 136 patients (21.2%), and in the lower third in 235 patients (36.5%).

**Table 8. Demographics and clinical characteristics of patients treated with percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction. Reprinted by permission from Springer Nature.**

Characteristic	Patients, n (%)	1-year survival, n (%)	Median survival months (95% CI)	p-value <sup>1</sup>
All	643 (100)	108 (16.8%)	2.6 (2.2–3.0)	
Age				0.012
≤75 years	433 (67.3)	80 (18.5)	3.0 (2.4–3.6)	
>75 years	210 (32.7)	28 (13.3)	2.0 (1.5–2.5)	
Sex				0.39
Female	317 (49.3)	54 (17.0)	2.8 (2.3–3.4)	
Male	326 (50.7)	54 (16.6)	2.3 (1.7–2.9)	
Comorbidities				0.73
Yes	446 (69.4)	79 (17.7)	2.6 (1.5–3.7)	
No	197 (30.6)	29 (14.7)	2.6 (2.2–3.0)	
ASA class <sup>2</sup>				<0.001
1–2	159 (24.7)	38 (23.9)	5.0 (3.2–6.8)	

Characteristic	Patients, n (%)	1-year survival, n (%)	Median survival months (95% CI)	p-value <sup>1</sup>
3	399 (62.1)	66 (16.5)	2.5 (2.0–3.1)	
4	75 (11.7)	3 (4.0)	0.9 (0.2–1.5)	
ECOG PS				<0.001
0–1	283 (44.0)	81 (28.6)	6.5 (5.2–7.8)	
2	194 (30.2)	17 (8.8)	1.7 (1.4–2.1)	
3–4	166 (25.8)	10 (6.0)	0.9 (0.7–1.2)	
Cancer				<0.001
Primary	480 (74.7)	97 (20.2)	3.5 (3.0–4.0)	
Metastatic	163 (25.3)	11 (6.7)	1.5 (1.2–1.8)	
Primary cancer				0.11
Pancreatic	246 (51.2)	41 (16.7)	3.4 (2.5–4.4)	
Cholangiocellular	175 (36.5)	45 (25.7)	4.2 (3.0–5.5)	
Gallbladder	35 (7.3)	5 (14.3)	2.9 (2.4–3.3)	
Hepatocellular	14 (2.9)	2 (14.3)	2.0 (0.1–3.9)	
Other	10 (2.1)	4 (40.0)	2.0 (0.2–3.8)	
Metastatic cancer				0.19
Gastric	52 (31.9)	5 (9.6)	1.5 (0.6–2.5)	
Colorectal	43 (26.4)	3 (7.0)	1.3 (0.7–1.8)	
Other	68 (41.7)	3 (4.4)	1.3 (0.9–1.7)	
Level of bile duct obstruction				0.19
Upper (hilum)	272 (42.3)	50 (18.4)	2.3 (1.9–2.8)	
Middle (Common hepatic duct)	136 (21.2)	13 (9.6)	2.8 (2.0–3.6)	
Lower (common bile duct)	235 (36.5)	45 (19.1)	3.3 (2.2–4.3)	
Bilirubin level after PTBD <sup>3</sup>				<0.001
<60.0 µmol/L	247 (41.2)	50 (20.2)	4.0 (3.1–4.9)	
≥60.0 µmol/L	352 (58.8)	54 (15.3)	2.0 (1.6–2.4)	
Time period				0.028
1999–2004	188 (29.2)	26 (13.8)	2.4 (1.6–3.2)	
2005–2010	219 (34.1)	27 (12.3)	2.2 (1.6–2.8)	
2010–2016	236 (36.7)	55 (23.3)	3.1 (2.3–3.8)	

ASA class: American Society of Anesthesiologists physical status classification, ECOG PS: Eastern Cooperative Oncology Group performance status, PTBD: percutaneous transhepatic biliary drainage, <sup>1</sup> Log-rank, <sup>2</sup> missing data for 10 patients, <sup>3</sup> missing data for 44 patients.

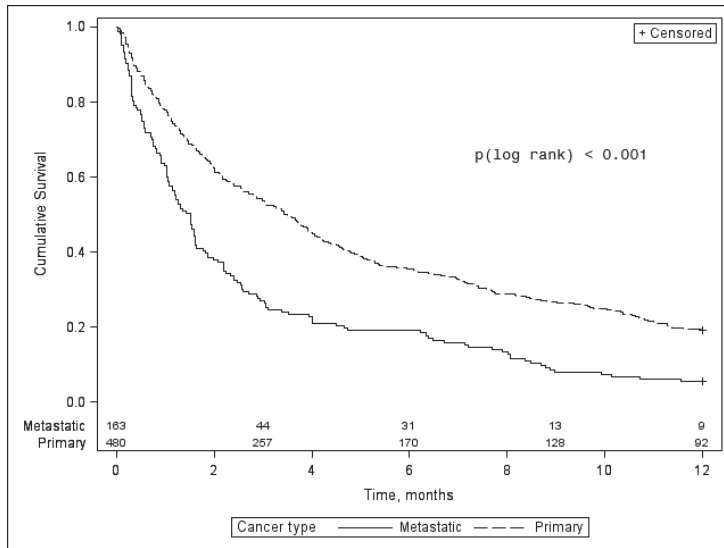
The median overall survival after drainage was 2.6 months (95% CI: 2.2–3.0), and 108 patients (16.8%) were alive at one year after drainage. Univariate analyses

revealed that higher median survival times were associated with age  $\leq 75$  years, lower ASA class, lower ECOG PS, obstruction due to primary cancer, and bilirubin level  $< 60.0 \mu\text{mol/L}$  within 30 days after PTBD as well as time period being most favorable during the last period between 2011 and 2016 (Table 8). The time period was taken into account in the multivariable Cox regression model, which revealed that shorter survival time was associated with metastatic cancer, ECOG PS  $\geq 2$ , ASA class 4, and bilirubin level within 30 days after PTBD  $\geq 60.0 \mu\text{mol/L}$  (Table 9). Figures 5–7 show survival analysis according to etiology of bile duct obstruction (Figure 5), ECOG PS (Figure 6), and ASA class (Figure 7).

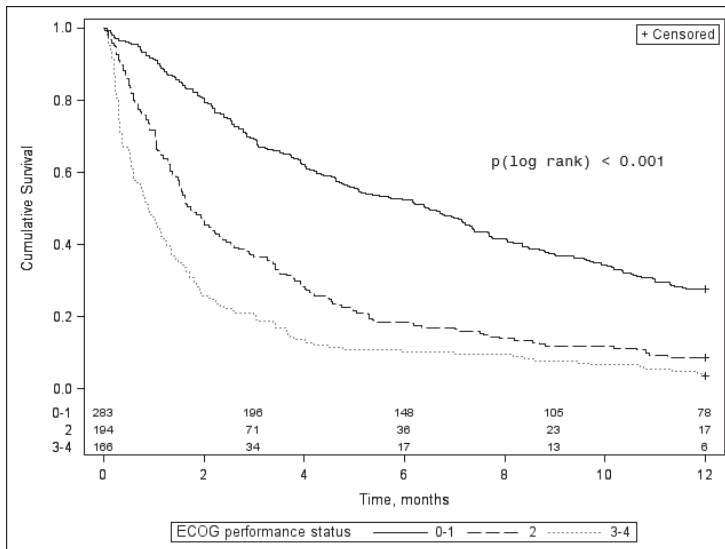
**Table 9. Multivariable Cox regression analysis of factors associated with 1-year mortality after percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction. Reprinted by permission from Springer Nature.**

Characteristic	HR	95% CI	p-value <sup>1</sup>
Time period			
2011–2016	1.0		
1999–2004	1.4	1.1–1.7	0.007
2005–2010	1.4	1.2–1.8	0.001
Cancer			
Primary	1.0		
Metastatic	2.2	1.8–2.7	<0.001
ECOG PS			
0–1	1.0		
2	2.3	1.8–2.8	<0.001
3–4	3.5	2.8–4.4	<0.001
ASA class			
1–2	1.0		
3	1.3	1.0–1.6	0.29
4	2.1	1.5–2.9	<0.001
Bilirubin level after PTBD			
$< 60.0 \mu\text{mol/L}$	1.0		
$\geq 60.0 \mu\text{mol/L}$	1.3	1.1–1.6	0.003

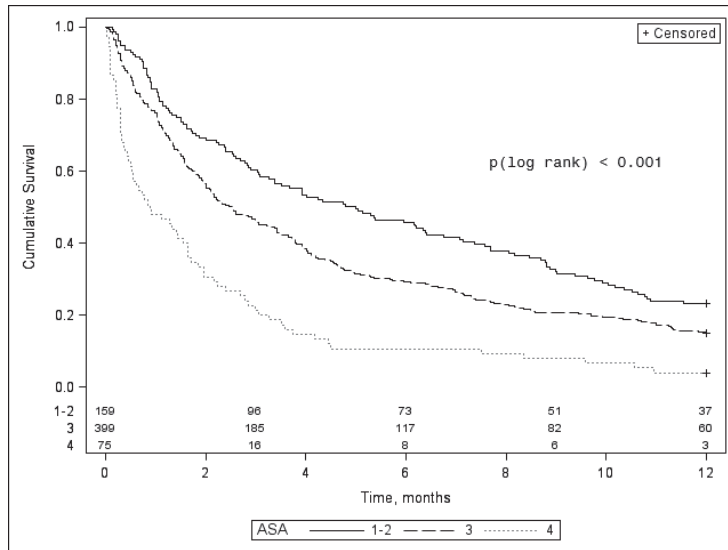
HR: hazard ratio, CI: confidence interval, ASA class: American Society of Anesthesiologists physical status classification, ECOG PS: Eastern Cooperative Oncology Group performance status, PTBD: percutaneous transhepatic biliary drainage, <sup>1</sup> p-value according to multivariable Cox regression model.



**Fig. 5. Kaplan-Meier 1-year survival analysis of patients after percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction according to cancer type.**



**Fig. 6. Kaplan-Meier 1-year survival analysis of patients after percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction according to ECOG performance status.**



**Fig. 7. Kaplan-Meier 1-year survival analysis of patients after percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction according to ASA classification.**

## 5.2 Study II

The study group comprised 588 patients with malignant biliary obstruction, of which 258 patients (43.9%) had pancreatic cancer, 222 (37.7%) had biliary tract cancer, and 108 (18.4%) had metastasis from cancers of the gastrointestinal tract of, which 52 (48.1%) had gastric cancer and 43 (39.8%) had colorectal cancer. A SEMS was inserted in 455 patients (77.4%), a plastic stent with combined ERCP was used in 18 patients (3.1%), and external drainage was performed in 115 patients (19.5%). After PTBD, surgery was carried out for 37 patients (6.3%); of which resection of cancer was performed for 15 patients (2.6%), biliary bypass for 9 patients (1.5%) and explorative laparotomy for 13 patients (2.2%).

Patient demographics and clinical characteristics are presented in Table 10. The study groups were as follows: 156 patients (26.5%) had cholangitis before PTBD, 215 patients (36.6%) had cholangitis after PTBD, and 217 patients (36.9%) did not have cholangitis. The most common cancer in patients with cholangitis before PTBD and patients without cholangitis was pancreatic cancer ( $n=69$ , 44.2% and  $n=107$ , 49.3%;  $p=0.043$ ), whereas in the patients with cholangitis after PTBD it was biliary tract cancer ( $n=98$ , 45.6%;  $p=0.043$ ). In both cholangitis groups, the

obstruction was most often in the upper level of the bile duct (41.7% and 49.8%), whereas in the no cholangitis group it was most often in the lower level of the bile duct (42.9%;  $p=0.029$ ). Patients without cholangitis had fewer complications related to PTBD (28.6%;  $p<0.001$ ). The most common complication was bleeding ( $n=198$ , 33.7%), and in most cases was seen as a hemobilia. Most of the complications ( $n=204$ , 85.4%) were treated conservatively, and relatively few patients ( $n=35$ , 14.6%) were treated with interventional radiology or surgery. Laboratory values are presented in Table 11. The proportion of positive blood cultures did not differ in patients with cholangitis before PTBD and cholangitis after PTBD (44/106 [41.5%] vs. 56/143 [39.2%];  $p=0.80$ ).

**Table 10. Demographics and clinical characteristics of patients treated with percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction.**

Characteristic	No cholangitis	Cholangitis before PTBD	Cholangitis after PTBD	p-value <sup>1</sup>
All, n=588	n=217 (36.9%)	n=156 (26.5%)	n=215 (36.6%)	
Age, years; mean (SD[range])	71 (10[40–91])	70 (11[38–90])	69 (12[26–93])	0.097 <sup>2</sup>
Sex, male	93 (42.9)	93 (59.6)	114 (53.0)	0.005
Comorbidities				0.26
0	68 (31.3)	46 (29.5)	58 (27.0)	
1–2	104 (47.9)	65 (41.7)	110 (51.2)	
>2	45 (20.7)	45 (28.8)	47 (21.9)	
ECOG PS				<0.001
0–1	100 (46.1)	45 (28.8)	116 (54.0)	
2	69 (31.8)	54 (34.6)	56 (26.0)	
3–4	48 (22.1)	57 (36.5)	43 (20.0)	
ASA-class <sup>3</sup>				0.16
1–2	46 (21.6)	34 (22.2)	65 (30.7)	
3	143 (67.1)	99 (64.7)	129 (60.8)	
4	24 (11.3)	20 (13.1)	18 (8.5)	
Cancer				0.043
Pancreatic	107 (49.3)	69 (44.2)	82 (38.1)	
Biliary tract	70 (32.3)	54 (34.6)	98 (45.6)	
Metastatic gastrointestinal	40 (18.4)	33 (21.2)	35 (16.3)	
Level of bile duct obstruction				0.029
Upper (hilum)	75 (34.6)	65 (41.7)	107 (49.8)	
Middle (common hepatic duct)	49 (22.6)	33 (21.2)	42 (19.5)	
Lower (common bile duct)	93 (42.9)	58 (37.2)	66 (30.7)	
Bilirubin level after PTBD <sup>4</sup>				0.42

Characteristic	No cholangitis	Cholangitis before	Cholangitis after	p-value <sup>1</sup>
		PTBD	PTBD	
<60.0 µmol/L	74 (40.0)	67 (45.0)	80 (38.1)	
Severity of cholangitis <sup>5</sup>				0.15
Mild		104 (66.7)	163 (75.8)	
Moderate		41 (26.3)	42 (19.5)	
Severe		11 (7.1)	10 (4.7)	
Complications of PTBD				
All	62 (28.6)	72 (46.2)	105 (48.8)	<0.001
Bleeding	53 (24.4)	58 (37.2)	87 (40.5)	<0.001
Other <sup>6</sup>	8 (3.7)	20 (12.8)	21 (9.8)	0.004

Data are the number of patients (%), unless otherwise noted. PTBD: percutaneous transhepatic biliary drainage, ASA class: American Society of Anesthesiologists physical status classification, SD: standard deviation, ECOG PS: Eastern Cooperative Oncology Group performance status,<sup>1</sup> Pearson chi-squared test, except for age, <sup>2</sup> analysis of variance test, <sup>3</sup> missing data for 10 patients, <sup>4</sup> missing data for 44 patients, <sup>5</sup> according to Tokyo Guidelines 2013, <sup>6</sup> pleuritis, pneumonia, biliary or duodenal perforation, peritonitis or pancreatitis.

**Table 11. Laboratory values of patients with malignant biliary obstruction and cholangitis before or after percutaneous transhepatic biliary drainage (PTBD).**

Laboratory test	Median values (Percentiles 25–75)		p-value <sup>1</sup>
	Before PTBD, n=156	After PTBD, n=215	
Leukocyte, 10 <sup>9</sup> /L	11.1 (7.9–14.9)	13.0 (9.8–17.4)	0.035
C-reactive protein (CRP) mg/L	121 (78–169)	160 (118–215)	<0.001
Alanine aminotransferase, U/L	123 (72–197)	72 (46–111)	0.016

The table shows laboratory values taken within 2 days after diagnosis of cholangitis. Missing data 20%. No statistically significant differences were found between the groups in the following laboratory values: hemoglobin, thrombocyte, thromboplastin time international ratio (TT-INR), creatinine, albumin, and bilirubin. Data was not shown. PTBD: percutaneous transhepatic biliary drainage, <sup>1</sup> Student's t-test.

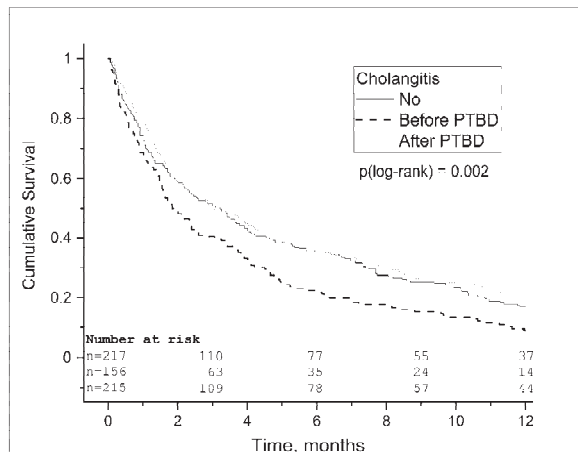
The outcome of 588 patients according to the onset and severity of the cholangitis are presented in Table 12. The 30-day mortality rate was 30.8% (n=48) in patients with cholangitis before PTBD, 19.5% (n=42) in patients with cholangitis after PTBD, and 25.8% (n=56) in patients without cholangitis (p=0.002). The patients without cholangitis and complications had a 30-day mortality rate of 21.9% (n=34). Median survival was 1.8 months among patients with cholangitis before PTBD, 3.0 months among patients with cholangitis after PTBD, and 3.2 months among patients without cholangitis (p=0.002). One year after PTBD, 9.0% (n= 14) of the patients with cholangitis before PTBD were alive, 20.5% (n=44) of the patients with cholangitis after PTBD were alive, and 17.1% (n=37) of the patients without

cholangitis were alive (p=0.002). Figure 8 shows a survival analysis of patients according to onset of cholangitis and Figure 9 shows a survival analysis of patients according to severity of cholangitis.

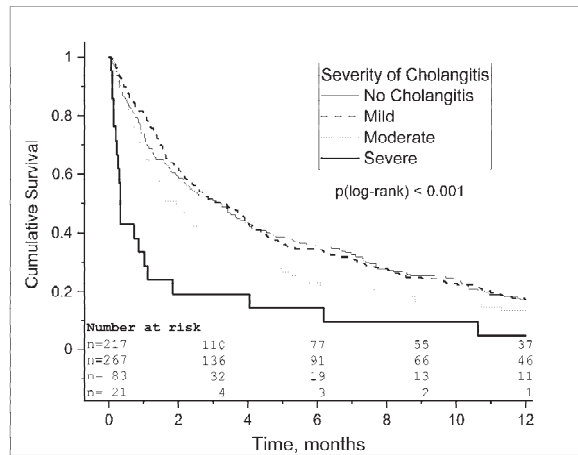
**Table 12. Outcome of patients with malignant biliary obstruction after percutaneous transhepatic biliary drainage (PTBD) according to the onset and severity of the cholangitis.**

Characteristic	30-day mortality, n (%)	p-value <sup>1</sup>	Median survival months (95% CI)	1-year survival, n (%)	p-value <sup>1</sup>
All, n=588	146 (24.8)		2.7 (2.2–3.2)	95 (16.2)	
Onset of cholangitis		0.039			0.002
No cholangitis, n=217, 36.9%	56 (25.8)		3.2 (2.4–4.1)	37 (17.1)	
Before PTBD, n=156, 26.5%	48 (30.8)		1.8 (1.2–2.4)	14 (9.0)	
After PTBD, n=215, 36.6%	42 (19.5)		3.0 (2.2–3.8)	44 (20.5)	
Severity of cholangitis <sup>2</sup>		<0.001			<0.001
Mild, n=267, 72.0%	50 (18.7)		3.3 (2.5–4.0)	46 (17.2)	
Moderate, n=83, 22.4%	26 (31.3)		1.9 (1.2–2.6)	11 (13.3)	
Severe, n=21, 5.6%	14 (66.7)		0.3 (0.3–0.4)	1 (4.8)	

CI: confidence interval, PTBD: percutaneous transhepatic biliary drainage, <sup>1</sup> Log Rank, <sup>2</sup> According to Tokyo Guidelines 2013.



**Fig. 8. Kaplan-Meier 1-year survival analysis of patients after percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction according to onset of cholangitis.**



**Fig. 9. Kaplan-Meier 1-year survival analysis of patients after percutaneous transhepatic biliary drainage (PTBD) for malignant biliary obstruction according to severity of cholangitis based on the Tokyo Guidelines 2013.**

The HR for 1-year mortality for patients with cholangitis before PTBD was 1.3 (95% CI 1.06–1.67;  $p=0.015$ ) compared to the patients with cholangitis after PTBD in the multivariable adjusted Cox regression model. When patients without cholangitis were used as the reference group, the HR for 1-year mortality was 1.24 (95% CI 0.99–1.56;  $p=0.062$ ) for the patients who had cholangitis before PTBD and 0.94 (95% CI 0.75–1.17;  $p=0.56$ ) for those who had cholangitis after PTBD. Correspondingly, the HR for 30-day mortality was 1.03 (95% CI 0.69–1.54;  $p=0.89$ ) for the patients who had cholangitis before PTBD and 0.69 (95% CI 0.46–1.04;  $p=0.079$ ) for the patients who had cholangitis after PTBD.

After successful PTBD, 54 out of 291 patients (18.6%) received chemotherapy: 10 out of 81 patients (12.3%) with cholangitis before PTBD, 24 out of 105 patients (22.9%) with cholangitis after PTBD and 20 out of 105 patients (19.0%) without cholangitis. After initiation of chemotherapy, the median survival times were 5.2 months (95% CI 1.2–9.1) for patients with cholangitis before PTBD, 9.4 months (95% CI 3.9–15.0) for patients with cholangitis after PTBD and 15.3 months (95% CI 5.8–24.8) for patients without cholangitis ( $p=0.12$ ).

### 5.3 Study III

The study group comprised 158 patients with malignant biliary obstruction, of which 82 (51.9%) had pancreatic cancer and 76 (48.1%) had biliary tract cancer. A SEMS was inserted in 125 (79.1%) patients, and external drainage was used in 33 (20.9%) patients. The diagnosis of cancer was verified by histology in 40 patients (25.3%), by cytology in 88 patients (55.7%) and by radiology in 30 patients (19.0%). The median time from cancer diagnosis to drainage was 0.3 months (25th–75th percentiles 0.2–0.7 months). After PTBD, 12 patients (7.6%) underwent surgery; of which resection was performed for 4 patients (2.5%), biliary bypass for 4 patients (2.5%) and explorative laparotomy for 4 patients (2.5%).

Patient demographics and clinical characteristics are presented in Table 13. Patients in the best supportive care group were older than those in the chemotherapy group (mean ages 76 vs. 68 years;  $p < 0.001$ ). ECOG PS grade 1–2 ( $p < 0.001$ ) were more common in the chemotherapy group than in the best supportive care group.

After PTBD, 62 (39.2%) patients were evaluated by an oncologist. Their median bilirubin level after PTBD was 33.5  $\mu\text{mol/L}$  (IQR=18.8–52.8  $\mu\text{mol/L}$ ). Thirty-two (51.6%) of these 62 patients received chemotherapy, while 30 patients (48.4%) did not receive chemotherapy for the following reasons: 16 patients had ECOG PS 3, 10 patients had ECOG PS 4 and four patients with ECOG PS 1–2 refused chemotherapy. Ninety-six (60.8%) patients from the study population were not evaluated by an oncologist and their median bilirubin level after PTBD was 90.0  $\mu\text{mol/L}$  (IQR=45.5–229.0  $\mu\text{mol/L}$ ; missing values for 11 patients). The main exclusion criteria for evaluation of chemotherapy in addition to high bilirubin level were poor performance status, advanced disease, age, co-morbidities, and patient refusal.

Among the 32 (20.3%) patients who received chemotherapy, 17 (53.1%) had pancreatic cancer and 15 (46.9%) had biliary tract cancer. The corresponding figures in the best supportive care group were 65 (51.6%) and 61 (48.4%), respectively. The median time for the initiation of chemotherapy after PTBD was 1.8 months (IQR=0.7–4.6 months). Single-agent gemcitabine was the first-line treatment for 76% (13/17) of patients with pancreatic cancer and 73% (11/15) of patients with biliary tract cancer. Combination chemotherapy was given to 24% (4/17) of patients with pancreatic cancer (gemcitabine with oxaliplatin or erlotinib, etoposide with cisplatin, or fluorouracil with oxaliplatin and irinotecan) and 27% (4/15) of patients with biliary tract cancer (gemcitabine with cisplatin). Only two

patients with pancreatic cancer and one patient with biliary tract cancer received a second-line treatment. No patient received a third-line treatment.

**Table 13. Demographics and clinical characteristics of patients. Reprinted by permission from International Institute of Anticancer Research.**

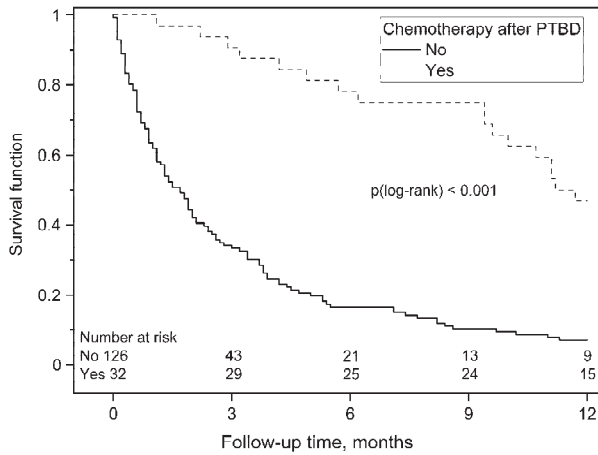
Characteristic	Chemotherapy, n=32 (20.3%)	Best supportive care, n=126 (79.7%)	p-value <sup>1</sup>
Age, years; mean (SD [range])	68 (7.4 [52-82])	76 (9.2 [49-93])	<0.001 <sup>2</sup>
Sex, male	22 (68.8)	50 (39.7)	0.003
Comorbidities			0.16
0	13 (40.6)	34 (27.0)	
1–2	15 (46.9)	59 (46.8)	
>2	4 (12.5)	33 (26.2)	
Cancer			0.88
Pancreatic	17 (53.1)	65 (51.6)	
Biliary tract	15 (46.9)	61 (48.4)	
ASA class			0.008
1–2	12 (37.5)	21 (16.7)	
3	20 (62.5)	89 (70.6)	
4	0 (0)	16 (12.7)	
ECOG PS			<0.001
0–1	27 (84.4)	34 (27.0)	
2	4 (12.5)	46 (36.5)	
3–4	1 (3.1)	46 (36.5)	
Level of bile duct obstruction			0.53
Upper (hilum)	12 (37.5)	47 (37.3)	
Middle (common hepatic duct)	8 (25.0)	22 (17.5)	
Lower (common bile duct)	12 (37.5)	57 (45.2)	

Data represent the number of patients (%) unless otherwise noted. SD: standard deviation, ASA class: American Society of Anesthesiologists physical status classification, ECOG PS: Eastern Cooperative Oncology Group performance status, <sup>1</sup> Pearson chi-squared test, except for age, <sup>2</sup> Student's t-test.

The median survival of the 32 patients treated with chemotherapy was 11.7 months, and 15 (46.9%) patients were alive at 1 year after PTBD ( $p < 0.001$ ). Both cancer groups were associated with significant survival benefits with chemotherapy, with a median survival of 11.2 months for the patients with pancreatic cancer and 15.1 months for the patients with biliary tract cancer. The median survival of the 126 patients treated with best supportive care was 1.7 months ( $p < 0.001$ ); 2.0 months in patients with ECOG PS 0–2, and 0.9 months with ECOG PS 3–4 ( $p = 0.216$ ). Nine (7.1%) of the patients with best supportive care were alive at 1 year after PTBD.

Figure 10 shows a survival analysis and Table 14 shows the outcome of 158 patients with pancreatic or biliary tract cancer according to therapy after PTBD.

According to the time-dependent multivariable adjusted Cox regression model, the HR for 1-year mortality was 0.22 (95% CI 0.12–0.41;  $p < 0.001$ ) for patients who received chemotherapy compared to patients who received best supportive care.



**Fig. 10. Kaplan–Meier survival analysis of patients with pancreatic or biliary tract cancer according to therapy after percutaneous transhepatic biliary drainage (PTBD). Reprinted by permission from International Institute of Anticancer Research.**

**Table 14. Outcome after percutaneous transhepatic biliary drainage (PTBD) in patients with pancreatic or biliary tract cancer. Reprinted by permission from International Institute of Anticancer Research.**

Therapy after PTBD	Median survival, months (95% CI)	1-year survival, n (%)	p-value <sup>1</sup>
Chemotherapy, n=32 (20.3%)			
Overall	11.7 (9.0–14.5)	15 (46.9)	<0.001
Pancreatic cancer, n=17 (53.1%)	11.2 (10.2–12.1)	7 (41.2)	
Biliary tract cancer, n=15, (46.9%)	15.1 (5.2–25.0)	8 (53.3)	
Best supportive care, n=126 (79.7%)			
Overall	1.7 (1.2–2.2)	9 (7.1)	<0.001
Pancreatic cancer, n=65 (51.6%)	1.3 (0.6–2.1)	3 (4.6)	
Biliary tract cancer, n=61, (48.4%)	1.9 (1.2–2.6)	6 (9.8)	

CI: confidence interval, <sup>1</sup> Log rank test between patient groups of chemotherapy, and with best supportive care after PTBD.

## **6 Discussion**

### **6.1 Methodological considerations and generalization of the results**

The aim of the study was to clarify challenging treatment of the patients with malignant biliary obstruction. Patients with malignant biliary obstruction usually have a poor prognosis due to their advanced disease. In daily clinical practice there is a heterogenous group of patients with different malignancies and status of disease that should be taken into account when evaluating treatment options.

The study population of 643 patients treated with PTBD for malignant biliary obstruction represents one of the largest studies on this topic and is well representative of daily clinical practice; and thus, the data is appropriate for investigating research questions. All procedures and treatments were performed by experienced radiologists, anesthesiologists, gastrointestinal surgical and oncological teams. Morbidity and mortality related to PTBD were in line with previous studies (Tapping et al., 2011; Uberoi et al., 2012; Rees et al., 2020).

The study population consisted of a heterogenous group of patients with different diseases and phases of disease that were taken into account in the planning of the studies and in the selection of the appropriate methods to be used.

The study was conducted in a tertiary center university hospital. The results of the study can be generalized to centers with experienced multidisciplinary teams for the treatment of malignant biliary obstructions with PTBD.

#### **6.1.1 Strengths of the study**

In studies II and III a DAG were constructed to examine biases related to all possible causal variables to create a minimally sufficient adjustment in the multivariable model to avoid misleading conclusions and validate the study groups more comparably. Considering the pitfalls of variable selection methods based on statistical significance, it has been recommended to avoid using stepwise and univariable analyses, as they are susceptible to bias and produce inadequate inferences (Talbot & Massamba, 2019). Causal DAGs are frameworks for researchers for visualizing the variables that play a role in causal questions and are used to examine biases related to causal interference and to determinate covariate adjustment sets for minimizing confounding bias (Textor et al., 2016; Etmann,

Collins, & Mansournia, 2020). Furthermore, we took into account of immortal time bias, i.e. the time between diagnosis and the initiation of treatment. If this time period is not accounted for analysis, immortal time bias will cause misleading conclusions (Suissa, 2008; Agarwal et al., 2018; Newman et al., 2020). In study III, a multivariable adjusted time-dependent model was used, which is accurate in estimating treatment effects and includes all patients in the study, to avoid and minimize the immortal time bias on survival.

### **6.1.2 Limitations of the study**

The main limitation of the study was that it was a single-center, retrospective study, similar to most previous studies on this topic. The study population consisted of a heterogeneous group of patients with different malignancies and phases of disease. The research material collection time was 16 years, which was reflected in the results; during the last six years the patients had significantly better outcomes than previous years. Indications for PTBD were similar during the study period. Actually, this outcome benefit was associated with primary tumors, which is explained by the development and use of chemotherapy. Due to the retrospective nature of the study tumors could not have been reliably classified according to the TNM-classification system (Brierley, Gospodarowicz, & Wittekind, 2017), and therefore this information is missing. Furthermore, in a retrospective study, the effect of the procedure and treatments on the patient's quality of life could not be assessed. Study III included a relatively small number of patients receiving chemotherapy.

## **6.2 Discussion of the main results**

### **6.2.1 Survival and predictive factors on outcome in patients with malignant biliary obstruction treated with PTBD**

Patients with malignant biliary obstruction have a poor prognosis due to their advanced disease. Study I showed that the overall median survival of all cohorts was only 2.6 months after PTBD, which is in line with previous findings (please see studies shown in Table 4 and Table 6). In patients with biliary obstruction due to primary cancer, median survival was 3.5 months, which was two times higher than among patients with metastatic cancers. Contradictory results have been reported in studies focused on malignant biliary obstruction caused by metastases

of gastric or colorectal cancer with the overall median survival of 2.3 to 6.0 months (Migita et al., 2009; Gwon et al., 2012; Kasuga et al., 2012, Hong et al., 2013; Sellier et al., 2017). The general condition of the patient is important for the prognosis after PTBD. In our study, ECOG PS and ASA class were independent predictors of survival. Patients with ECOG PS 3–4 and ASA class 4 had a poor prognosis with a median survival 0.9 months, which agrees with previous studies (Neal et al., 2010; Crosara Teixeira et al., 2013; Ferraz Goncalves et al., 2020). After drainage, patients with high bilirubin levels can achieve clinically relevant reductions in bilirubin (Levy et al., 2016). The post-drainage bilirubin level has been found to be a significant predictor of prognosis reflecting successful drainage and our patients with post-drainage bilirubin values of  $<60 \mu\text{mol/L}$  within 30 days after PTBD had a longer survival than shown in the findings of similar previous literature (Brountzos et al., 2007).

### **6.2.2 *The impact of cholangitis on survival in patients with gastrointestinal cancer and malignant biliary obstruction treated with PTBD***

Study II showed that the survival of the patients with cholangitis before PTBD was poorer compared to patients with cholangitis after PTBD, whose survival did not differ from patients without cholangitis. To the best of our knowledge, only sparse information exists on evaluating the impact of cholangitis before or after PTBD on the long-term survival of patients with malignant biliary obstruction. In earlier studies (please see Table 4), the impact of cholangitis on survival has not been systematically analyzed and reported, and only overall survivals in the study populations were reported without distinction between patients with or without cholangitis.

Most earlier studies concerning acute cholangitis have focused on the in-hospital or 30-day mortality (Li et al., 2015; Kiriyaama et al., 2017; Sha et al., 2019; Laviglegrand et al., 2021). In a recent retrospective multicenter study of patients with acute cholangitis treated in intensive care units, the hospital mortality rate was 29%; a malignant obstruction and timing of drainage after 48 hours were both associated with mortality (Laviglegrand et al., 2021). In our series, the median delay before drainage was 5.5 days. These two determinants – malignancy and late drainage – will increase mortality and also explain the high 30-day mortality rate of 30.8% in our study population. Thus, earlier biliary drainage would have probably improved survival in our series. Furthermore, the advanced stage of

malignancy and progression may lead to acute cholangitis and thus worsen the prognosis; however, due to the retrospective nature of our study tumors could not have been reliably classified for analysis. We were not able to clarify why in our series the 30-day mortality rate in cholangitis after PTBD was lower (19.5%) than among patients without cholangitis (25.8%). It is noteworthy that in our study, the 30-day mortality rate among patients without cholangitis or other complications was as high as 21.9%, reflecting the severity and complexity of underlying malignancy in 30-day mortality in patients with malignant obstruction treated with PTBD. Therefore, it is important to take into account the cause of obstruction and state of malignancy when analyzing the etiology of 30-day mortality. In a multicenter observational study, the 30-day mortality rate of acute cholangitis in patients with malignant biliary obstruction was 7.2%, when patients who were considered to have died directly from malignancy were excluded (Kiriyama et al., 2017).

Cholangitis within 24 hours after PTBD is common with about 25% of cases in our study and in a previous study (Ahn et al., 2013). The high incidence of cholangitis soon after the procedure highlights the importance of antibiotic prophylaxis (Ryan, Ryan, & Smith, 2004; Sutcliffe et al., 2015). However, antimicrobial prophylaxis does not seem to be a comprehensive solution, because approximately 80% of the patients in our series received antimicrobial prophylaxis of cefuroxime and in the study by Ahn et al. (2013) patients mainly received cefotaxime before PTBD. There are two earlier studies where the incidence of cholangitis after PTBD has been clearly lower (11.1% and 15.7%) (Li et al., 2015; Saluja et al., 2008). In these studies, the duration of antimicrobial prophylaxis (cefoperazone/sulbactam or ciprofloxacin) was three days after PTBD. So, it seems possible that one dose of prophylaxis before PTBD is not sufficient for prevention of cholangitis after the procedure for patients with malignant biliary obstruction. Furthermore, antibiotic agents used in the abovementioned studies are more active against Gram-negative bacteria than cefuroxime. The overall incidence of cholangitis after PTBD in our series was as high as 49.8%, which is clearly higher than in earlier studies where it has varied from 8.4% to 36.1% (Li et al., 2015; Zu et al., 2019; Sha et al., 2019). Higher incidence may be at least partly due to the fact that about half of our patients with cholangitis after PTBD had hilar biliary obstruction, which is more challenging than distal obstruction with regard to achieving complete drainage (Iacono, 2013; Moole et al., 2016), and is more often associated with infection (Motte et al., 1991; Nennstiel et al., 2015).

### **6.2.3 The survival benefit of chemotherapy compared to best supportive care after PTBD**

The results of study III showed that patients with pancreatic or biliary tract cancer and malignant biliary obstruction treated with PTBD and thereafter chemotherapy had significantly better survival compared to those treated with best supportive care after drainage. The subset of fit patients who received chemotherapy after PTBD had 6.9 times better survival compared to patients who received best supportive care. In the best supportive care group survival difference was only 1 month between patient with ECOG PS 0–2 and ECOG 3–4. Thus, good performance status, per se, may not explain the difference in survival between chemotherapy and best supportive care groups. To the best of our knowledge, this was the first study analyzing the benefit of chemotherapy in patients with malignant biliary obstruction after PTBD including both pancreatic and biliary tract cancer, the most common causes of hyperbilirubinemia due to malignancy. Survival benefit was also seen in patients with cholangitis; although survival rate remains lower in patients who had cholangitis before PTBD.

The median overall survival of patients with biliary tract cancer who received best supportive has been from 2.5 to 5.7 months (Jansen et al., 2020). In a recent retrospective study, the median survival was 12.8 months in 34 patients with hilar cholangiocarcinoma, who received gemcitabine combined with cisplatin after drainage compared to 6.1 months in 74 patients with best supportive care (Shin et al., 2020). In our study, only four out of the 15 patients in the group with biliary tract cancer group received the combination treatment; while 11 patients received gemcitabine alone. The median survival was 15.1 months for our patients with biliary tract cancer with chemotherapy after PTBD and 1.9 months for those who received best supportive care. The survival may have been even better if the gemcitabine-cisplatin combination with good results had been used in study patients more widely since 2010 (Valle et al., 2010).

The combination of nab-paclitaxel and gemcitabine has been shown to be an effective first line treatment in phase III trial with improving survival of patients with locally advanced and metastatic pancreatic cancer (Vogel et al., 2016; Kieler et al., 2020). In the present study, 13 out of 17 patients (76%) with pancreatic cancer received gemcitabine alone as a first-line treatment. Still, the median survival of our patients with pancreatic cancer treated with chemotherapy was 11.2 months and with best supportive care 1.3 months. The survival figures may have been better

with the more active use of the combination therapy for fit patients (Pelzer et al., 2018).

Also, after successful biliary drainage in patients with metastatic colorectal or gastric cancer survival improves significantly in patients who receive subsequent systemic chemotherapy (Migita et al., 2009; Kasuga et al., 2012; Kastelijns et al., 2021).

Limited knowledge is available regarding appropriate chemotherapy dosing and management in patients with higher bilirubin levels. Treatment recommendations for patients with hyperbilirubinemia have been based on small phase I studies or retrospective patient series with heterogeneous study populations (Valle et al., 2010; Conroy et al., 2011; Lamarca et al., 2015; Vogel et al., 2015; Alvarez et al., 2018; Dierks et al., 2017; Pelzer et al., 2018; Rogers et al., 2020). Chemotherapy may be considered even with higher bilirubin levels than in present daily clinical practice (i.e. <1.5-fold ULN). It has been reported that an initial dose reduction is unnecessary for widely used gemcitabine or capecitabine in patients with biliary tract or pancreatic cancer after successful management of biliary obstruction, even with moderate hyperbilirubinemia (Joerger et al., 2014; Shibata et al., 2016). A combination of nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer and hyperbilirubinemia has been reported to be a feasible and safe treatment option with respect to individualized dose administrations, and there is an ongoing prospective trial (AIO-PAK-0117 PANCHO) for evaluating this combination (Pelzer et al., 2018).

In a large retrospective cohort study 13% to 27% of patients received chemotherapy after PTBD (Rees et al., 2020). In our patient series less than 20% of the patients received chemotherapy after successful biliary drainage. Study III showed that only approximately 40% of the patients were evaluated by an oncologist and half of them received chemotherapy. It is important that the success of drainage is systematically monitored after the procedure. An oncological evaluation is important to identify patients eligible for chemotherapy. According to the latest knowledge concerning hyperbilirubinemia and chemotherapy, more patients in our series may have been eligible to receive and benefit from chemotherapy after PTBD. Further studies are needed to clarify this challenging clinical problem.

### **6.3 Clinical importance of the study**

Patients with advanced malignancy and biliary obstruction treated with PTBD have a poor prognosis. The results of this study highlight the importance of the evaluation for chemotherapy after PTBD in the treatment of these patients. Patients who were able to receive chemotherapy after successful PTBD had months of survival benefit compared to patients with only best supportive care. Treatment of cholangitis with biliary drainage in addition to antimicrobial treatment are crucial for improving survival. The predictive factors (ECOG PS, ASA class, cholangitis, metastatic cancer and successful drainage) found in this study should be taken into account when evaluating appropriate treatment for patients. Multidisciplinary teams play an important role in evaluating the treatment options for this kind of complex disease and systematic oncological evaluation is important to identify patients for chemotherapy. Best supportive care should be an essential part of the treatment, and patients who are not eligible for chemotherapy should be referred to palliative care.

### **6.4 Future treatment and study expectations**

The most challenging aspect of treatment of patients with malignant biliary obstruction, especially for the elderly, is determining the goal of the treatment; intent of curative treatment, intent to improve life expectancy or intent to relieve symptoms, improve quality of life and preserve independence. This is emphasized in daily clinical practice when there is a heterogenous group of patients with different malignancies and phases of disease.

The goal of biliary drainage is to relieve symptoms and improve quality of life and also enable chemotherapy treatment by reducing high bilirubin level. However, PTBD is an invasive procedure and complications may, at worst, impair the prognosis of these patients. Therefore, the patient's performance status, age, disease progression and potential complications of PTBD should be taken into account, especially if the patient is asymptomatic. Of note is that the survival benefit of surgery, radiation and chemotherapy may be diminished with age (Ogden, Xie, Ma, & Hubbard, 2018). Furthermore, elderly patients have high a risk of toxicity due to chemotherapy and need careful monitoring of treatment (Feliu et al., 2018).

Due to the high risk of organ dysfunction associated with cholangitis, early diagnosis and treatment of cholangitis with urgent biliary drainage in addition to antimicrobial treatment are crucial for improving survival among patients with

malignant biliary obstruction and acute cholangitis. Respectively, antibiotic prophylaxis before the PTBD procedure, close monitoring of patients after PTBD and early initiation of antimicrobial treatment are important. A prospective patient series would provide more understanding of the proper antibiotic prophylaxis to prevent PTBD-associated cholangitis and the treatment of cholangitis.

Prospective studies in which patients are evaluated in multidisciplinary teams are needed to optimize the treatment of this heterogenous and complex group of patients. Further studies are needed for developing appropriate guidelines for chemotherapy in patients with malignant biliary obstruction and hyperbilirubinemia. However, there are clinically important issues that cannot be addressed in the context of randomized trials. Studies based on a nationwide prospective registry in which clinical data including quality of life is systematically collected could clarify these issues.

## 7 Conclusions

1. Patients with malignant biliary obstruction have a poor prognosis with an overall median survival of 2.6 months after PTBD. The independent factors predicting poor survival were metastatic cancer, ECOG PS  $\geq 2$ , high ASA class 4, and bilirubin level after PTBD  $\geq 60.0$   $\mu\text{mol/L}$ .
2. Patients with cholangitis before PTBD have poorer survival (1.8 months) compared to patients with cholangitis after PTBD (3.0 months), whose survival did not significantly differ from patients without cholangitis (3.2 months).
3. After PTBD, patients with pancreatic or biliary tract cancer that received chemotherapy showed significantly better survival (11.7 months) than patients that received only best supportive care (1.7 months). Several months of survival benefit with chemotherapy was also seen in patients with cholangitis after successful biliary drainage and antimicrobial treatment.



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## Original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

- I Niemelä, J., Kallio, R., Ohtonen, P., Perälä, J., Saarnio, J., & Syrjälä, H. (2018). Is palliative percutaneous drainage for malignant biliary obstruction useful? *World Journal of Surgery*, 42(9), 2980-2986. <https://doi.org/10.1007/s00268-018-4567-0>
- II Niemelä, J., Kallio, R., Ohtonen, P., Saarnio, J., & Syrjälä, H. Impact of cholangitis on survival of patients with malignant biliary obstruction treated with percutaneous transhepatic biliary drainage. Manuscript.
- III Niemelä, J., Syrjälä, H., Ohtonen, P., Saarnio, J., & Kallio, R. (2021). Chemotherapy improves survival after percutaneous biliary drainage in patients with pancreatic or biliary tract cancer with biliary obstruction. *Anticancer Research*, 41(6), 2979-2984. <https://doi.org/10.21873/anticanres.15079>

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Original publications are not included in the electronic version of this dissertation.



1655. Kiiskilä, Jukka (2022) Association of mitochondrial DNA haplogroups with endurance performance
1656. Kyrklund, Mikael (2022) Antibody response to oxidized epitopes and oral bacteria in atherosclerosis
1657. Salin, Janne (2022) Luokkahuoneen sisäilman mikrobien ja pölyn toksisuudet lisäävät opettajien työympäristöön liittyvien oireiden riskiä : poikkileikkaus-tutkimus
1658. Kanavakis, Georgios (2022) Associations of facial profile and occlusion in the Northern Finland Birth Cohort 1966
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1666. Roivainen, Petri (2022) Kiireettömien ensihoitotehtävien hoidon tarpeen arviointi puhelinsairaanhoidajan toteuttamana
1667. Nurkkala, Juho (2022) Commencement of nutrition support during critical illness and after major surgery
1668. Kamakura, Remi (2022) A novel system for delivery of nutritional compounds to regulate appetite
1669. Björnholm, Lassi (2022) Early predictors of white matter microstructure in the adult brain
1670. Lehtilahti, Maria (2022) Charcot-Marie-Tooth Disease : Molecular epidemiology in Northern Ostrobothnia

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ISBN 978-952-62-3290-4 (Paperback)  
ISBN 978-952-62-3291-1 (PDF)  
ISSN 0355-3221 (Print)  
ISSN 1796-2234 (Online)