

Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma

Citation for published version (APA):

Coelen, R. J. S., Roos, E., Wiggers, J. K., Besselink, M. G., Buis, C. I., Busch, O. R. C., Dejong, C. H. C., van Delden, O. M., van Eijck, C. H. J., Fockens, P., Gouma, D. J., Koerkamp, B. G., de Haan, M. W., van Hooft, J. E., IJzermans, J. N. M., Kater, G. M., Koornstra, J. J., van Lienden, K. P., Moelker, A., ... van Gulik, T. M. (2018). Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma: a multicentre, randomised controlled trial. *The Lancet Gastroenterology and Hepatology*, 3(10), 681-690. [https://doi.org/10.1016/S2468-1253\(18\)30234-6](https://doi.org/10.1016/S2468-1253(18)30234-6)

Document status and date:

Published: 01/10/2018

DOI:

[10.1016/S2468-1253\(18\)30234-6](https://doi.org/10.1016/S2468-1253(18)30234-6)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma: a multicentre, randomised controlled trial



Robert J S Coelen*, Eva Roos*, Jimme K Wiggers, Marc G Besselink, Carlijn I Buis, Olivier R C Busch, Cornelis H C Dejong, Otto M van Delden, Casper H J van Eijck, Paul Fockens, Dirk J Gouma, Bas Groot Koerkamp, Michiel W de Haan, Jeanin E van Hooft, Jan N M IJzermans, G Matthijs Kater, Jan J Koonstra, Krijn P van Lienden, Adriaan Moelker, Steven W M Olde Damink, Jan-Werner Poley, Robert J Porte, Rogier J de Ridder, Joanne Verheij, Victor van Woerden, Erik A J Rauws, Marcel G W Dijkgraaf, Thomas M van Gulik†

Summary

Background In patients with resectable perihilar cholangiocarcinoma, biliary drainage is recommended to treat obstructive jaundice and optimise the clinical condition before liver resection. Little evidence exists on the preferred initial method of biliary drainage. We therefore investigated the incidence of severe drainage-related complications of endoscopic biliary drainage or percutaneous transhepatic biliary drainage in patients with potentially resectable perihilar cholangiocarcinoma.

Methods We did a multicentre, randomised controlled trial at four academic centres in the Netherlands. Patients who were aged at least 18 years with potentially resectable perihilar cholangiocarcinoma requiring major liver resection, and biliary obstruction of the future liver remnant (defined as a bilirubin concentration of $>50 \mu\text{mol/L}$ [2.9 mg/dL]), were randomly assigned (1:1) to receive endoscopic biliary drainage or percutaneous transhepatic biliary drainage through the use of computer-generated allocation. Randomisation, done by the trial coordinator, was stratified for previous (attempted) biliary drainage, the extent of bile duct involvement, and enrolling centre. Patients were enrolled by clinicians of the participating centres. The primary outcome was the number of severe complications between randomisation and surgery in the intention-to-treat population. The trial was registered at the Netherlands National Trial Register, number NTR4243.

Findings From Sept 26, 2013, to April 29, 2016, 261 patients were screened for participation, and 54 eligible patients were randomly assigned to endoscopic biliary drainage ($n=27$) or percutaneous transhepatic biliary drainage ($n=27$). The study was prematurely closed because of higher mortality in the percutaneous transhepatic biliary drainage group (11 [41%] of 27 patients) than in the endoscopic biliary drainage group (three [11%] of 27 patients; relative risk 3.67, 95% CI 1.15–11.69; $p=0.03$). Three of the 11 deaths among patients in the percutaneous transhepatic biliary drainage group occurred before surgery. The proportion of patients with severe preoperative drainage-related complications was similar between the groups (17 [63%] patients in the percutaneous transhepatic biliary drainage group vs 18 [67%] in the endoscopic biliary drainage group; relative risk 0.94, 95% CI 0.64–1.40). 16 (59%) patients in the percutaneous transhepatic biliary drainage group and ten (37%) patients in the endoscopic biliary drainage group developed preoperative cholangitis ($p=0.1$). 15 (56%) patients required additional percutaneous transhepatic biliary drainage after endoscopic biliary drainage, whereas only one (4%) patient required endoscopic biliary drainage after percutaneous transhepatic biliary drainage.

Interpretation The study was prematurely stopped because of higher all-cause mortality in the percutaneous transhepatic biliary drainage group. Post-drainage complications were similar between groups, but the data should be interpreted with caution because of the small sample size. The results call for further prospective studies and reconsideration of indications and strategy towards biliary drainage in this complex disease.

Funding Dutch Cancer Foundation.

Copyright © 2018 Elsevier Ltd. All rights reserved.

Introduction

Perihilar cholangiocarcinoma is a rare tumour originating in the bile ducts at the liver hilum, which typically causes biliary obstruction.¹ Surgical resection, through the use of combined extrahepatic bile duct resection and extended liver resection, offers a median survival of 19–39 months.² Extended liver resection in

cholestatic patients is associated with postoperative mortality of up to 18%.^{2–5} Preoperative biliary drainage aims to reduce jaundice, which decreases bacterial translocation and improves nutritional status, liver function, immune dysfunction, and the ability of the liver to regenerate after resection.^{6,7} Consequently, preoperative biliary drainage can reduce postoperative

Lancet Gastroenterol Hepatol 2018; 3: 681–90

Published Online
August 16, 2018
[http://dx.doi.org/10.1016/S2468-1253\(18\)30234-6](http://dx.doi.org/10.1016/S2468-1253(18)30234-6)

See [Comment](#) page 657

*Contributed equally

†Collaborators listed in the appendix

Department of Surgery (R J S Coelen MD, E Roos MD, J K Wiggers MD, Prof M G Besselink MD, Prof O R C Busch MD, Prof D J Gouma MD, Prof T M van Gulik MD), **Department of Pathology** (J Verheij MD), **Department of Radiology** (Prof O M van Delden MD, K P van Lienden MD), **Department of Gastroenterology and Hepatology** (Prof P Fockens MD, J E van Hooft MD), and **Clinical Research Unit and Department of Clinical Epidemiology, Biostatistics and Bioinformatics** (Prof M G W Dijkgraaf PhD), **Amsterdam University Medical Center, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands**; **Department of Surgery** (C I Buis MD, Prof R J Porte MD), **Department of Radiology** (G M Kater MD), and **Department of Gastroenterology** (J J Koonstra MD), **University Medical Center Groningen, University of Groningen, Groningen, Netherlands**; **Department of Surgery and School of Nutrition and Translational Research in Metabolism** (Prof C H C Dejong MD, Prof S W M O Damink MD, V van Woerden MD), **Department of Radiology** (Prof M W de Haan MD), and

Department of Gastroenterology (R J de Ridder MD), Maastricht University Medical Center, Maastricht, Netherlands; Department of Surgery, Universitätsklinikum Aachen, Aachen, Germany (Prof C H C Dejong, Prof S W M O Damink, V van Woerden); and Department of Surgery (Prof C H J van Eijck MD, B G Koerkamp MD, Prof J N M IJzermans MD), Department of Radiology and Nuclear Medicine (A Moelker MD), and Department of Gastroenterology and Hepatology (J-W Poley MD), Erasmus University Medical Center, Rotterdam, Netherlands

Correspondence to: Prof Thomas M van Gulik, Department of Surgery, Amsterdam University Medical Centre, Amsterdam 1100 DD, the Netherlands
t.m.vangulik@amc.nl

See Online for appendix

Research in context

Evidence before this study

Perihilar cholangiocarcinoma is a rare tumour originating in the bile ducts at the liver hilum, which typically causes biliary obstruction. Biliary drainage is recommended to treat obstructive jaundice and optimise clinical condition before liver resection. The two most commonly used drainage techniques are endoscopic biliary drainage and percutaneous transhepatic biliary drainage. A previous retrospective study reported fewer complications after initial percutaneous drainage as compared with endoscopic drainage. Before the start of the present trial, no prospective studies had been done. We searched PubMed, Embase, MEDLINE, and Cochrane, between Feb 1, 2013, and March 1, 2013, without date or language restrictions, for studies including the terms “hilar cholangiocarcinoma”, “proximal bile duct cancer”, and “biliary drainage”. Findings from another retrospective series from Japan also showed favourable results after percutaneous biliary drainage.

Added value of this study

In this multicentre, randomised controlled trial, we randomly assigned 54 patients with jaundice because of perihilar

cholangiocarcinoma to undergo either endoscopic or percutaneous transhepatic biliary drainage before a major liver resection. The trial was prematurely closed because of higher mortality in the percutaneous transhepatic biliary drainage group. To our knowledge, this is the first prospective trial in an unselected group of patients with potentially resectable perihilar cholangiocarcinoma. Despite early termination, the trial provides insight into this complex disease.

Implications of all the available evidence

Although previous retrospective studies suggested that percutaneous biliary drainage is beneficial in patients with perihilar cholangiocarcinoma, the present trial was terminated at 50% accrual because of high mortality in the percutaneous transhepatic biliary drainage group. Furthermore, a recent meta-analysis and retrospective study acknowledged the occurrence of severe postoperative complications after the percutaneous approach. These results call for reconsideration of indications for and strategy towards biliary drainage in this complex disease.

mortality, especially in extended liver resections.⁸ Nonetheless, biliary drainage can be harmful when drainage-related complications, such as cholangitis, further deteriorate the patient's condition and increase the risk of postoperative mortality.^{9–11} These complications potentially outweigh the benefits of biliary drainage, and should be minimised to optimise surgical outcomes.

The two most commonly used drainage techniques are endoscopic biliary drainage and percutaneous transhepatic biliary drainage (referred to as endoscopic drainage and percutaneous drainage hereafter). Currently, no consensus has been reached on the preferred method of preoperative biliary drainage in patients with perihilar cholangiocarcinoma. The incidence of complications after endoscopic drainage and percutaneous drainage has only been assessed in small retrospective series, which reported higher technical success and fewer complications after percutaneous drainage than endoscopic drainage.^{12,13} Because these studies might be biased by patient selection, randomised trials are needed to confirm the potential benefit of preoperative percutaneous transhepatic biliary drainage compared with endoscopic biliary drainage. Therefore, we did a multicentre, randomised trial investigating the incidence of severe drainage-related complications of both techniques in patients with potentially resectable perihilar cholangiocarcinoma.

Methods

Study design

The trial was a multicentre, randomised controlled trial that aimed to show superiority of percutaneous transhepatic biliary drainage over endoscopic biliary

drainage as the initial preoperative biliary drainage procedure in patients with perihilar cholangiocarcinoma. The study was done at four academic centres that treat most patients with perihilar cholangiocarcinoma in the Netherlands: Amsterdam University Medical Centre, Amsterdam; Erasmus University Medical Centre, Rotterdam; University Medical Centre Groningen, Groningen; and Maastricht University Medical Centre, Maastricht. The institutional review board at each institution approved the protocol. An independent data and safety monitoring board, comprising a surgeon, gastroenterologist, and clinical epidemiologist, was assigned to evaluate the progress of the trial and examine the unblinded safety variables after 50% accrual. Annual unblinded safety reports including serious adverse events were provided to the institutional review board by the trial steering committee. The complete methods and research have been published previously,¹⁴ and are included in the appendix (pp 3–8).

Participants

All patients with presumed perihilar cholangiocarcinoma who were referred to the multidisciplinary teams at each centre were screened for eligibility. Perihilar cholangiocarcinoma was defined as a tumour originating in the common hepatic duct, at the hepatic duct confluence, or in the left or right hepatic duct on imaging (CT or magnetic resonance cholangiopancreatography, or both).¹⁵ Patients who were aged at least 18 years, had a resectable tumour that required major hepatectomy based on imaging, and had biliary obstruction of the future liver remnant were included in the study. Criteria

for resectable perihilar cholangiocarcinoma were an anticipated complete (R0) resection with adequate future liver remnant (>30%) and no arterial involvement. Biliary obstruction was defined as a total bilirubin concentration of at least 50 µmol/L (2.9 mg/dL) before drainage. Patients with a previous endoscopic drainage attempt in the referring hospital were also eligible for randomisation. The choice to include these patients was made on the basis of daily clinical practice emphasising a real-life design. When patients present with jaundice, endoscopic retrograde cholangiopancreatography is often done on the suspicion of biliary stones, and drainage attempts then often fail. These patients were eligible for inclusion if they had a persistently elevated total bilirubin concentration of more than 50 µmol/L (because of insufficiently draining stent or no stent), or persistent biliary dilatation in the future liver remnant on imaging.

The objective of both endoscopic biliary drainage and percutaneous transhepatic biliary drainage was to drain the future liver remnant only. The type of liver resection and anticipated future liver remnant were established in the multidisciplinary team meeting. Pathological confirmation of perihilar cholangiocarcinoma before surgery was not required.

Exclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance score of 3 or higher, technical contraindications for either endoscopic biliary drainage or percutaneous transhepatic biliary drainage, incomplete clinical recovery from side-effects of previous stenting attempts, and signs of active cholangitis.

All participants provided written informed consent.

Randomisation and follow-up

Patients were randomly assigned (1:1) to endoscopic biliary drainage or percutaneous transhepatic biliary drainage by minimisation through the use of computer-generated allocation. To equally distribute possible confounders over groups, randomisation was stratified for previous (attempted) biliary drainage, the extent of bile duct involvement (Bismuth-Corlette classification), and enrolling centre. Randomisation was done by the trial coordinator (RJSC). Patients were enrolled by clinicians of the participating centres. Biliary drainage was done within 5 days after randomisation.

Further preoperative work-up consisted of staging laparoscopy at the discretion of the surgeon, and portal vein embolisation in patients with a small future liver remnant (<30%). Patients who were randomly assigned, but who did not undergo resection after randomisation were included in the analysis. Final study follow-up was scheduled at 90 days after surgery.

Procedures

Preoperative biliary drainage preferably consisted of drainage of the future liver remnant. In patients requiring portal vein embolisation, the indication for bilateral drainage was evaluated by the multidisciplinary team.¹⁶

Endoscopic biliary drainage procedures were done by experienced gastroenterologists, and percutaneous transhepatic biliary drainage procedures by experienced interventional radiologists. The technique and antibiotic prophylactic protocol are described in the appendix (pp 6–7). After percutaneous transhepatic biliary drainage, bile was externally drained during the first 48 h, after which the drain was capped for full internal drainage. External drainage of percutaneous drains was allowed in the event of suspected cholangitis. Repeat procedures were allowed if adequate drainage of the future liver remnant was not achieved or complications occurred. Crossover treatment was allowed if the allocated procedure was not feasible. Crossover to percutaneous transhepatic biliary drainage was mandatory if endoscopic biliary drainage failed after two attempts.

Technical success of biliary drainage was defined as achievement of internal biliary drainage of the future liver remnant segments. Follow-up with ultrasound and measurement of total bilirubin concentration was done 7 days later. Therapeutic success was defined as normal calibre bile ducts in the future liver remnant on ultrasound examination and a decrease in total bilirubin concentration of at least 20% at day 7 relative to the concentration at randomisation. To evaluate adequacy of biliary drainage, additional total bilirubin assessments were done at 14 days after technical success, and at admission for exploratory laparotomy.

Exploratory laparotomy was done 4–6 weeks after randomisation. A radical resection was done if the diagnosis of locally resectable perihilar cholangiocarcinoma without distant metastases was found at laparotomy. Resections consisted of excision of the liver hilum and the extrahepatic bile ducts en bloc with (extended) hemihepatectomy including the caudate lobe, and complete lymphadenectomy of the hepatoduodenal ligament. Portal vein excision with reconstruction was used only when the tumour infiltrated into the portal vein bifurcation. If present, transhepatic percutaneous drains were routinely left in situ and used as trans-anastomotic drains. External drainage was allowed to decompress the biliary-enteric anastomoses in the first 5–7 days after surgery. In the event of locally advanced tumours or distant metastases precluding a curative-intent resection, palliative cholecystectomy or gastroenterostomy, or both, was done if indicated by the surgeon. These patients usually underwent palliative stenting with metal biliary stents before discharge.

Outcomes

The primary outcome was the number of severe drainage-related complications between randomisation and exploratory laparotomy. Severe complications were defined as any complication leading to additional invasive interventions, admission to hospital, or death (definitions in appendix, p 4), assessed by data managers at each centre under supervision of the local principal investigator. For

For more on computer-generated allocation see www.aleaclinical.eu

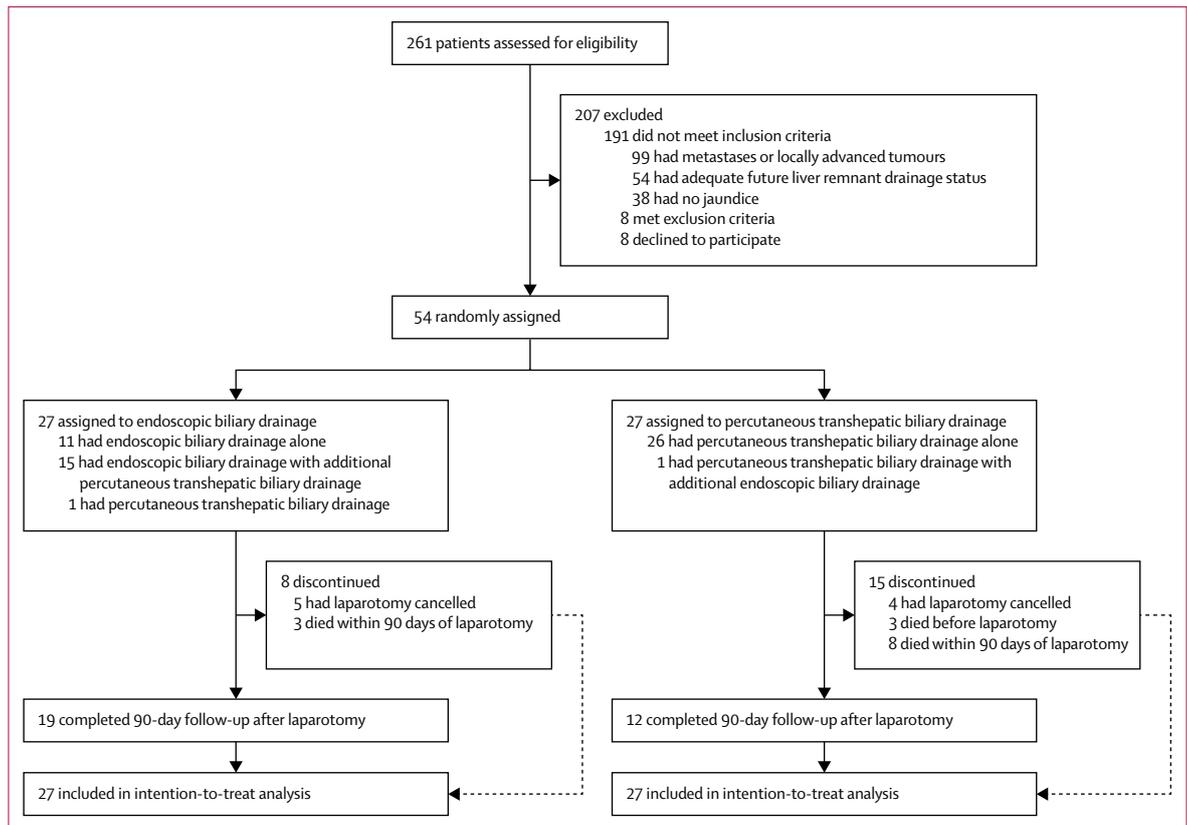


Figure: Trial profile

patients who did not undergo exploratory laparotomy, the number of drainage-related complications was measured until 7 days after the decision to cancel exploratory laparotomy or 90 days after randomisation, whichever came first. To exclude bias in the determination of events pertaining to the primary outcome measure, the study was designed with a masked endpoint assessment. A masked adjudication committee reviewed all adverse events and evaluated whether complications were severe according to the predefined definitions. Determination of the severity of a complication was not subject to judgment of the clinicians or investigators.

Secondary outcomes included measures of the technical and therapeutic success of biliary drainage, quality of life, and 90-day postoperative morbidity and mortality (see appendix, p 4, for full list).

All baseline and outcome data were collected by designated independent data managers at each site using a standardised case record form (appendix, pp 9–29). The study coordinator, statistician, and lead academic author analysed the data and were responsible for the completeness and accuracy of the analyses.

Statistical analysis

The principal analysis consisted of an intention-to-treat comparison of the number of preoperative severe drainage-related complications in both groups, using a

Mann-Whitney *U* test for ordered categorical data with a two-sided 0.05 significance level. The proportion of patients with any severe drainage-related complication was also expressed in terms of relative risk (RR) and 95% CIs. Categorical variables were evaluated using Pearson's χ^2 test or Fisher's exact test.

Sample size calculation resulted in 106 patients. On the basis of previous data, complications were expected to occur in 50% of cases after endoscopic biliary drainage and in 25% of cases after percutaneous biliary drainage and this estimation was further expanded with proportions for the number of complications (appendix, p 7).^{12,14} Per group, 53 patients were needed to achieve a power of 80% to detect a difference with a two-sided significance level of 0.05 and accounting for 3% patient dropout.

Quality-of-life scores from available assessments during follow-up were analysed using descriptive statistics with mean difference, with baseline levels for successive measurements over time. Missing follow-up data were regarded as missing at random (appendix, p 42–44).

Statistical analyses were done with SPSS version 24.0. The trial was registered in the Netherlands National Trial Register (NTR4243).

Early termination

After the first annual progress report, fewer patients in the percutaneous drainage group completed full study

follow-up than in the endoscopic drainage group, and the institutional review board at the Amsterdam University Medical Center (trial coordinating centre) called for early data and safety monitoring board analysis. Mortality was found to be imbalanced between the groups, and because the safety monitoring board and trial steering committee did not find a causal relation, the safety monitoring board decided that if the imbalance increased at interim analysis and a satisfying explanation had not been found, the trial would be terminated. On interim analysis at 50% accrual, the mortality difference had increased and reached statistical significance. The data and safety monitoring board recommended the trial be stopped on the basis of higher mortality in the percutaneous transhepatic biliary drainage group than in the endoscopic biliary drainage group without clear cause (summary of data and safety monitoring board reports provided in appendix, p 36). All investigators met to discuss additional post-hoc subgroup analyses for mortality and crossover treatment. All outcome events that occurred in patients included in the trial before the date of trial termination were included in the analysis. Because of the small sample size, we used the Jonckheere-Terpstra test for ordered categorical data to establish whether the difference between the number of patients in both groups with zero to one, or two or more complications was statistically significant.

Role of the funding source

Funding for data management was received from the Dutch Cancer Foundation. The funder had no role in the study design, data collection, analysis, or interpretation of the data or the writing of the report. RJSC, ER, MGD, and TMvG had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

From Sept 26, 2013, to April 29, 2016, 261 patients were screened for participation; 54 eligible patients were randomly assigned to receive endoscopic biliary drainage (n=27) or percutaneous transhepatic biliary drainage (n=27; figure). Among the 191 patients who did not meet the inclusion criteria, 99 had metastases or locally advanced tumours on presentation, 54 had adequate future liver remnant drainage status, and 38 had no jaundice. One patient in the endoscopic biliary drainage group underwent percutaneous drainage because endoscopic drainage could not be done within 5 days for logistical reasons. Demographics and clinical characteristics of the study groups were similar at baseline (table 1). About a third of patients underwent a drainage attempt at the referring hospital before randomisation.

12 (22%) of the 54 patients did not have surgery. In the endoscopic drainage group, three patients had tumour progression (two with local progression, one with

	Endoscopic biliary drainage (n=27)	Percutaneous transhepatic biliary drainage (n=27)
Age, years	66 (60–72)	69 (64–73)
Sex		
Men	18 (67%)	18 (67%)
Women	9 (33%)	9 (33%)
Body-mass index, kg/m ²	24 (23–26)	25 (23–27)
ECOG performance score*		
0	9 (33%)	10 (37%)
1	9 (33%)	11 (41%)
2	6 (22%)	6 (22%)
Total bilirubin, µmol/L	249 (68–355)	280 (196–447)
C-reactive protein, mg/L	10 (6–19)	21 (15–32)
Leucocytes, 10 ⁹ /L	7·8 (7·2–10·3)	9·4 (8·0–11·2)
Tumour diameter, cm	2·6 (1·9–3·5)	2·5 (1·9–3·0)
Bismuth-Corlette type		
1	1 (4%)	0
2	3 (11%)	1 (4%)
3A	10 (37%)	12 (44%)
3B	4 (15%)	7 (26%)
4	9 (33%)	7 (26%)
Imaging		
CT	26 (96%)	26 (96%)
MRI	16 (59%)	16 (59%)
Drainage attempt before referral and enrolment	9 (33%)	8 (30%)
Type of drainage (endoscopic biliary drainage, percutaneous transhepatic biliary drainage)	8, 1	8, 0
More than one attempt	3	1
Anticipated future liver remnant left liver	18 (67%)	14 (52%)
Data are median (IQR); n (%); n, n; or n. *Eastern Cooperative Oncology Group (ECOG) scores were missing for three patients in the endoscopic biliary drainage group.		

Table 1: Demographics and clinical characteristics of the patients at baseline

pulmonary metastases), one patient was diagnosed with IgG4-related sclerosing cholangitis after 4 weeks, and another was considered unfit for surgery because of his pulmonary condition. In the percutaneous drainage group, seven patients did not have surgery; three patients had tumour progression (one with local progression, two with liver metastases), and one patient was considered unfit for surgery because of old age (81 years) and preoperative cholangitis. Three other patients in the percutaneous drainage group died of complications after biliary drainage and before surgery.

Two patients in the endoscopic group died within 90 days after resection. One patient in this group died within 90 days after surgery, but no resection was performed (unresectable tumour). Eight patients in the percutaneous transhepatic biliary drainage group (five within 90 days after resection) died after surgery. The difference in mortality from randomisation until 90-day follow-up after surgery between the percutaneous

	Endoscopic biliary drainage (n=27)	Percutaneous transhepatic biliary drainage (n=27)	p value
Initial procedure duration, min	50 (45–60)	35 (20–60)	0.06
Number of adequate stents placed	0.14
Failure to pass obstruction	7 (26%)	2 (7%)	..
1	13 (48%)	19 (70%)	..
2	7 (26%)	6 (22%)	..
Technical success	20 (74%)	25 (93%)	0.07
Therapeutic success*	17 (63%)	21 (78%)	0.21
Crossover treatment	15 (56%)	1 (4%)	<0.0001
Total number of procedures until surgery	0.04
1	4 (15%)	9 (33%)	..
2	15 (56%)	6 (22%)	..
≥3	8 (30%)	12 (44%)	..
Duration of percutaneous drain in situ until surgery, days	47 (35–62)	65 (51–80)	0.01
Total bilirubin at 1 week, µmol/L	91 (40–218)	164 (61–227)	0.22
Total bilirubin at 2 weeks, µmol/L	49 (28–102)	100 (67–166)	0.04
Surgery	n=22	n=20	..
Staging laparoscopy	6 (27%)	7 (35%)	0.59
Portal vein embolism	8 (36%)	5 (25%)	0.43
Time to surgery, days	49 (39–68)	65 (51–80)	0.07
Preoperative total bilirubin, µmol/L	21 (14–42)	19 (10–30)	0.47
Resections	n=12	n=11	..
Type of resection	0.42
Bile duct resection only	2 (17%)	0	..
Hemihepatectomy left	2 (17%)	5 (45%)	..
Hemihepatectomy right	2 (17%)	1 (9%)	..
Trisectionectomy left	2 (17%)	1 (9%)	..
Trisectionectomy right	4 (33%)	4 (36%)	..
Portal vein reconstruction	6 (50%)	6 (55%)	0.83
Blood loss, mL	2372 (1075–4375)	1450 (800–2500)	0.28
Number of hepaticojejunostomies	1.0
1	9 (75%)	9 (82%)	..
2	3 (25%)	2 (18%)	..
Transanastomotic drain	6 (50%)	11 (100%)	0.01

Data are median (IQR) or n (%). *Therapeutic success was defined as normal caliber bile ducts in the future liver remnant on ultrasound examination and at least a 20% decrease in total bilirubin level at day 7 compared with the reference at randomisation.

Table 2: Characteristics of preoperative biliary drainage and surgery

transhepatic biliary drainage group (11 [41%] of 27 patients) and endoscopic biliary drainage group (three [11%] of 27 patients; RR 3.67, 95% CI 1.15–11.69; $p=0.03$) resulted in termination of the trial at interim analysis, as recommended by the data and safety monitoring board.

The characteristics of biliary drainage and surgical procedures are listed in table 2. Technical success of biliary drainage was higher in the percutaneous drainage group than the endoscopic drainage group (93% vs 74%, $p=0.07$), with a shorter procedure duration (35 vs 50 min, $p=0.06$). Therapeutic success 1 week after biliary

drainage was 78% for percutaneous drainage and 63% for endoscopic drainage ($p=0.21$). Crossover in the endoscopic drainage group was high: 15 (56%) of 27 patients required additional percutaneous transhepatic biliary drainage because of technical failure ($n=7$), therapeutic failure ($n=2$), complications ($n=5$), or selective segmental branch biliary drainage ($n=1$). One patient in the percutaneous drainage group required additional endoscopic drainage to achieve internal drainage. The remaining 26 (96%) patients had successful internalisation of the percutaneous transhepatic biliary drainage. 41 (76%) of 54 patients had more than one drainage procedure between randomisation and surgery. Percutaneous transhepatic biliary drainage catheters, whether additionally placed in patients who had undergone endoscopic drainage or initially placed in patients who had undergone percutaneous drainage, remained longer in situ until surgery in the percutaneous transhepatic biliary drainage group (65 vs 47 days, $p=0.01$).

42 (78%) of the 54 patients had exploratory laparotomy, leading to a resection with curative intent in 23 (55%) of those patients ($n=12$ in the endoscopic biliary drainage group; $n=11$ in the percutaneous transhepatic drainage group). The median time from randomisation to surgery was 16 days shorter in the endoscopic drainage group than the percutaneous drainage group (49 vs 65 days, $p=0.07$), whereas the proportions of staging laparoscopy and portal vein embolisation were similar in both groups. Surgery was rescheduled because of drainage-related complications in four patients in each group. Of 23 resections, 11 (48%) patients had extended resections involving five or more liver segments, and 12 (52%) patients had portal vein reconstruction. These proportions were similar in both groups. Percutaneous drains remained in situ postoperatively in all patients in the percutaneous transhepatic biliary drainage group, whereas only six (50%) of 12 patients in the endoscopic biliary drainage group had a transanastomotic drain after crossover to percutaneous drainage. Malignancy was confirmed in 20 (87%) of 23 resection specimens; in the other three specimens, benign, inflammatory lesions were diagnosed.

Between randomisation and surgery, 17 (63%) of 27 patients in the percutaneous drainage group and 18 (67%) of 27 patients in the endoscopic drainage group developed one or more severe drainage-related complications (RR 0.94, 95% CI 0.64–1.40; absolute risk difference [ARD] 3.7%; table 3). The proportion of patients with more than one complication was similar between groups (Jonckheere-Terpstra test, $p=0.88$). The most frequent complication was cholangitis, which occurred in 16 (59%) patients in the percutaneous drainage group and ten (37%) patients in the endoscopic drainage group ($p=0.1$). Of the three patients who died after initial percutaneous transhepatic biliary drainage (before surgery), one died of cholangiosepsis with

subsequent liver failure, one died of hypovolaemic shock due to gastrointestinal bleeding, and one patient had therapy-resistant cholangitis and asked for euthanasia (appendix, p 38).

13 (65%) of 20 patients in the percutaneous drainage group and 12 (55%) of 22 patients in the endoscopic drainage group had severe complications within 90 days after exploratory laparotomy (RR 1.19, 95% CI 0.73–1.96; ARD 10.4%; table 4). 11 (26%) of 42 patients died within 90 days after exploratory surgery, three (14%) of 22 in the endoscopic biliary drainage group, and eight (40%) of 20 in the percutaneous transhepatic biliary drainage group (RR 2.93, 95% CI 0.91–9.55; ARD 26.4%). Among patients in the endoscopic drainage group who had exploratory laparotomy, 12 (55%) of 22 underwent resection; two (17%) of these patients died after resection, one of liver failure due to hepatic arterial thrombosis, and one due to disease progression (vertebral metastasis) after discharge. Ten (45%) of 22 patients in the endoscopic drainage group had unresectable perihilar cholangiocarcinoma at laparotomy, one of whom died of progressive disease. Among patients in the percutaneous drainage group who had exploratory laparotomy, 11 (55%) of 20 underwent resection; five (45%) of these patients died after resection. All patients in this group eventually died of severe complications resulting in liver failure, including two associated with sepsis after hepaticojejunostomy leakage (appendix, p 38). Nine (45%) of 20 patients in the percutaneous transhepatic biliary drainage group had unresectable disease at laparotomy, three of whom died within 90 days after surgery: two died of myocardial infarction and one of progressive disease.

Post-hoc, as-treated, and sub-group analyses were done for both complications and mortality, including in 37 patients who had not undergone a drainage attempt before inclusion (appendix, pp 39–41). Drainage naivety did not show a more favourable outcome in the percutaneous drainage group compared with the endoscopic drainage group (appendix, p 41). Patients who had both endoscopic and percutaneous drainage in the study (crossover group; n=16) had a lower risk of cholangitis and lower all-cause mortality than patients who underwent percutaneous drainage only (appendix, p 40).

Overall 90-day postoperative mortality among 100 patients with presumed resectable perihilar cholangiocarcinoma who were treated at the participating centres between 2013, and 2016, but were not included in the trial was 10% (appendix, p 37).

Available data on disease-specific (EORTC-QLQ-C30 and BIL-21) and generic quality of life (EQ-5D Visual Analogue scale) did not show a significant benefit for either of the allocated treatments (appendix, pp 42–44).

Discussion

This multicentre, randomised controlled trial of biliary drainage in patients with resectable perihilar cholangiocarcinoma was prematurely stopped because of

	Endoscopic biliary drainage (n=27)	Percutaneous transhepatic biliary drainage (n=27)	p value
Any complications	18 (67%)	17 (63%)	0.78*
Specific complications			
Cholangitis	10 (37%)	16 (59%)	0.10
Cholecystitis	1 (4%)	1 (4%)	1.00
Pancreatitis	5 (19%)	1 (4%)	0.19
Haemorrhage	1 (4%)	2 (7%)	1.00
Perforation	1 (4%)	0	1.00
Portal vein thrombosis	1 (4%)	0	1.00
Stent or drain dysfunction	5 (19%)	6 (22%)	0.74
Stent or drain dislocation	1 (4%)	5 (19%)	0.19
Death	0	3 (11%)	0.24
Number of complications	0.88†
0	9 (33%)	10 (37%)	..
1	11 (41%)	8 (30%)	..
≥2	7 (26%)	9 (33%)	..

Data are n (%). *Relative risk 0.94, 95% CI 0.64–1.40; absolute risk difference 3.7%. †Jonckheere-Terpstra test.

Table 3: Severe complications between randomisation and surgery

	Endoscopic biliary drainage (n=22)	Percutaneous transhepatic biliary drainage (n=20)	p value
Any complications	12 (55%)	13 (65%)	0.49*
Cholangitis	6 (27%)	3 (15%)	0.46
Intra-abdominal abscess	4 (18%)	2 (10%)	0.67
Wound infection	1 (5%)	1 (5%)	1.00
Pneumonia	0	1 (5%)	0.48
Haemorrhage	1 (5%)	2 (10%)	0.60
Portal vein thrombosis	0	1 (5%)	0.48
Biliary leakage	4 (18%)	2 (10%)	0.67
Liver failure	2 (9%)	5 (25%)	0.23
Relaparotomy	3 (14%)	5 (25%)	0.45
Death within 90 days			
With or without resection	3 (14%)	8 (40%)	0.08†
After resection	2 (17%; n=12)	5 (45%; n=11)	0.19

Data are n (%), or n (%; n). *Relative risk 1.19, 95% CI 0.73–1.96; absolute risk difference 10.4%. †Relative risk 2.93, 95% CI 0.91–9.55; absolute risk difference 26.4%.

Table 4: Severe complications within 90 days after surgery

increased mortality after percutaneous transhepatic biliary drainage, as compared with endoscopic biliary drainage. The incidence of severe complications was similar after endoscopic and percutaneous drainage.

We included patients in the trial who had a previous unsuccessful drainage attempt. Although this might have been a confounding factor, inclusion of these patients reflects the population that we see in clinical practice. Randomisation was stratified for this factor to ensure that the possible bias was similar and in the same direction across groups. The data and safety

monitoring board decided to terminate the trial at the interim analysis because of excess mortality in the percutaneous drainage group; although a clear cause was not identified, the increased mortality was deemed too large to ignore. We realise that the low patient numbers makes the study prone to type-I error. Therefore, although the results were prospectively collected and are, to our best efforts, corrected for bias, they should be interpreted with caution.

Compared with our own and other previous studies, the rates of drainage-related complications and mortality in the present study are substantially higher.^{12,13,17–19} However, previous studies only reported on a select group of patients who had adequate biliary drainage, exploratory laparotomy, and resection. Because of their retrospective nature, these studies are prone to selection bias that might have led to under-reporting of complications. The current randomised trial included all patients with presumed resectable perihilar cholangiocarcinoma at the time of presentation according to the intention-to-treat principle. Drainage-related complications leading to deteriorating clinical condition or early death, and unexpected advanced disease on additional staging contributed to the high 90-day all-cause mortality (26%) in the present study. All-cause mortality is usually not reported in retrospective series.

Our study showed the wide range of complications after biliary drainage for potentially resectable perihilar cholangiocarcinoma. Life-threatening complications, such as cholangiosepsis and bleeding, were observed before surgery. The proportion of patients who experienced post-drainage, pre-surgery complications were similar between the two groups (63% vs 67%). More drain dislocations and subsequent replacements were reported in the percutaneous drainage group than the endoscopic drainage group, possibly contributing to the longer interval between randomisation and surgery. Three patients in the percutaneous drainage group died of drainage-related complications before surgery. Despite conflicting low-level evidence, studies published in the past few years have acknowledged the occurrence of severe postoperative complications after previous percutaneous transhepatic biliary drainage.^{17,20} In one study,²¹ low-volume centres showed a higher occurrence of serious complications related to percutaneous drainage, whereas high-volume centres showed a similar proportion of complications between endoscopic and percutaneous drainage.

The overall 90-day mortality after resection was remarkably high (30%) when compared with similar patients not recruited during the trial period (10%). This result should be seen in view of the high number of patients who underwent extended liver resections with portal vein reconstruction in the current study. Although postoperative complications were similar in the two groups in this study, patients seemed less able to recover from these severe postoperative complications after percutaneous drainage.

Nevertheless, the increased mortality associated with initial percutaneous transhepatic biliary drainage in our trial was unexpected, and the cause remains unresolved. One hypothesis is that a type-I error occurred because of early termination of the trial or because of uncorrected or unknown confounding factors. Another hypothesis is that the externally draining bile leads to loss of bile acids from the enterohepatic cycle, which negatively affects liver function, liver regeneration, and immunity.^{22–26} Although internalisation of the percutaneous catheters was pursued in all patients, external drainage was often allowed in the event of cholangitis, or postoperatively, to decompress the biliary-enteric anastomosis. The loss of bile without adequate replacement perioperatively might have contributed to impaired immunity and suppression of the regenerative response, rendering patients prone to infectious complications and post-hepatectomy liver failure. Bacterial contamination of the biliary system after bile duct cannulation and a shift towards antibiotic-resistant species might contribute to this effect.²⁷ Patients who crossed over from endoscopic to percutaneous biliary drainage could be hypothesised to have had partial internal biliary drainage already, which might neutralise a potential harmful effect of percutaneous transhepatic drainage. In that sense, patients who needed both endoscopic and percutaneous biliary drainage because of an absence of therapeutic success appeared to be a reasonable in-between group with regard to mortality rate (ie, 13% in this group vs 9% and 41% in the endoscopic and percutaneous only groups, appendix p 40). The speculations on the role of bile loss and microbiome dysbiosis call for further research.

The study had several limitations. The inclusion of patients with previously failed or inadequate stenting (a third of the group) might have selected patients at risk for worse outcome and affected the outcome of subsequent procedures. However, in a sensitivity analysis excluding these patients, outcomes were not different (appendix, p 41). Additionally, the early termination of the trial resulted in a relatively small sample size that was underpowered for the primary outcome; as such, the data should be interpreted with caution. Some patients (13%) had advanced tumours or benign disease on additional staging after randomisation, which probably also affected survival outcomes. This is a well known problem in the work-up of potentially resectable perihilar cholangiocarcinoma.²⁸ Details on bile loss and bile cultures were not collected during the trial, thus reflecting standard care, but would have been valuable data to analyse.

The results of the present study call for further investigation of indications for and strategy towards biliary drainage in perihilar cholangiocarcinoma. Patients might benefit from endoscopic or percutaneous transhepatic biliary drainage depending on left or right bile duct involvement. Furthermore, the high number of complications might raise the question of whether

patients need biliary drainage at all. However, patients undergoing extended right hemihepatectomy have been shown to have a 22% risk of postoperative mortality when not drained, versus a 10% risk when drained.⁸ Without biliary drainage, evidence shows the regenerative capacity of the functional remnant liver is impaired, thereby impeding post-resection regeneration.^{29,30} Data published in the past 5 years suggest that a selected group of jaundiced patients who require resection of less than 50% of total liver volume do not benefit from preoperative biliary drainage in terms of having safer surgery.^{5,8,31} Because patients needing right-sided hepatectomy usually have less than 50% remnant liver, these patients might benefit from biliary drainage to decrease the risk of liver failure. For patients having left-sided resections with ample remnant liver volume, biliary drainage might not be beneficial. These presumptions need to be further assessed in prospective studies.

Perihilar cholangiocarcinoma is a complex tumour that should be managed in high-volume centres with experience in hepatobiliary diseases. Biliary drainage should not be done before resectability is assessed at a specialised centre, so the desired liver segments can be selectively drained on the basis of the surgical plan without subjecting patients to unnecessary additional procedures and associated risks.³² The presence of stents might disturb the imaging studies required to establish diagnosis and tumour extent. The extent to which the outcomes of our study might be prone to statistical bias, or whether they instead represent real-life effects caused by percutaneous transhepatic biliary drainage will hopefully be answered by the ongoing INTERCPT trial,³³ examining the optimal biliary drainage method in patients with perihilar cholangiocarcinoma.

In conclusion, in this randomised controlled trial comparing percutaneous transhepatic biliary drainage and endoscopic biliary drainage in patients with potentially resectable perihilar cholangiocarcinoma in four specialised centres, initial percutaneous transhepatic drainage was associated with higher mortality, although the incidence of drainage-related complications was similar in both groups. The trial was terminated at interim analysis, leaving several questions unanswered. Further prospective studies looking into this complex disease are urgently needed.

Contributors

RJSC contributed to design of the study; acquisition, analysis, and interpretation of data; drafting and revising the manuscript; and final approval of the manuscript. ER contributed to acquisition, analysis, and interpretation of data; drafting and revising the manuscript; and final approval of the manuscript. TMvG (principal investigator) contributed to conception and design of the study; acquisition and interpretation of data; drafting and revising the manuscript; and final approval of the manuscript. JKW contributed to conception and design of the study; acquisition and interpretation of data; revising the manuscript; and final approval of the manuscript. MGWD contributed to conception and design of the study; writing the statistical analysis plan; analysis, and interpretation of data; revising the manuscript; and final approval of the manuscript. EAJR contributed to conception and design of the study; acquisition and interpretation of data; revising the manuscript; and final approval of the manuscript. CHCD, CHJvE, and RJP (local site investigators) contributed

to conception and design of the study; acquisition of data; interpretation of data; revising the manuscript; and final approval of the manuscript. MGB, CIB, ORCB, OMvD, PF, DJG, MWdH, JEvH, JNMIJ, GMK, BGK, JJK, KPvL, AM, SWMOD, J-WP, RjdR, JV, and VvW contributed to acquisition of data; interpretation of data; revising the manuscript; and final approval of the manuscript. All authors agreed to be accountable for all aspects of the work.

Declaration of interests

PF reports personal fees from Boston Scientific, Cook Endoscopy, Fujifilm, Olympus, and Ethicon Endosurgery, all outside the submitted work. JEvH reports grants from Cook Endoscopy and Medtronic, personal fees from Boston Scientific and Abbott, all outside the submitted work. All other authors declare no competing interests.

Acknowledgments

Funding for data management was received from the Dutch Cancer Foundation (grant number UVA 2013–5925).

References

- 1 Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features. *Am J Med* 1965; **38**: 241–56.
- 2 Popescu I, Dumitrascu T. Curative-intent surgery for hilar cholangiocarcinoma: prognostic factors for clinical decision making. *Langenbeck's Arch Surg* 2014; **399**: 693–705.
- 3 Nuzzo G, Giulianti F, Ardito F, et al. Improvement in perioperative and long-term outcome after surgical treatment of hilar cholangiocarcinoma: results of an Italian multicenter analysis of 440 patients. *Arch Surg* 2012; **147**: 26–34.
- 4 Kaiser GM, Paul A, Sgourakis G, et al. Novel prognostic scoring system after surgery for Klatskin tumor. *Am Surg* 2013; **79**: 90–95.
- 5 Wiggers JK, Groot Koerkamp B, Cieslak KP, et al. Postoperative mortality after liver resection for perihilar cholangiocarcinoma: development of a risk score and importance of biliary drainage of the future liver remnant. *J Am Coll Surg* 2016; **223**: 321–31.e1.
- 6 van der Gaag NA, Kloek JJ, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Preoperative biliary drainage in patients with obstructive jaundice: history and current status. *J Gastrointest Surg* 2009; **13**: 814–20.
- 7 Yokoyama Y, Nagino M, Nimura Y. Mechanism of impaired hepatic regeneration in cholestatic liver. *J Hepatobiliary Pancreat Surg* 2007; **14**: 159–66.
- 8 Farges O, Regimbeau JM, Fuks D, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. *Br J Surg* 2013; **100**: 274–83.
- 9 Sakata J, Shirai Y, Tsuchiya Y, Wakai T, Nomura T, Hatakeyama K. Preoperative cholangitis independently increases in-hospital mortality after combined major hepatic and bile duct resection for hilar cholangiocarcinoma. *Langenbeck's Arch Surg* 2009; **394**: 1065–72.
- 10 Nagino M, Ebata T, Yokoyama Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. *Ann Surg* 2013; **258**: 129–40.
- 11 Yokoyama Y, Ebata T, Igami T, Sugawara G. The adverse effects of preoperative cholangitis on the outcome of portal vein embolization and subsequent major hepatectomies. *Surgery* 2012; **156**: 1190–96.
- 12 Kloek JJ, van der Gaag NA, Aziz Y, et al. Endoscopic and percutaneous preoperative biliary drainage in patients with suspected hilar cholangiocarcinoma. *J Gastrointest Surg* 2010; **14**: 119–25.
- 13 Kawakami H, Kuwatani M, Onodera M, et al. Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. *J Gastroenterol* 2011; **46**: 242–48.
- 14 Wiggers JK, Coelen RJ, Rauws EA, et al. Preoperative endoscopic versus percutaneous transhepatic biliary drainage in potentially resectable perihilar cholangiocarcinoma (DRAINAGE trial): design and rationale of a randomized controlled trial. *BMC Gastroenterol* 2015; **15**: 1–8.
- 15 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC cancer staging manual*, 7th edn. New York: Springer, 2010.

- 16 Dumonceau JM, Tringali A, Blero D, et al. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy* 2012; **44**: 277–98.
- 17 Hameed A, Pang T, Chiou J, et al. Percutaneous vs. endoscopic pre-operative biliary drainage in hilar cholangiocarcinoma—a systematic review and meta-analysis. *HPB* 2016; **18**: 400–10.
- 18 Al Mahjoub A, Menahem B, Fohlen A, et al. Preoperative biliary drainage in patients with resectable perihilar cholangiocarcinoma: is percutaneous transhepatic biliary drainage safer and more effective than endoscopic biliary drainage? A meta-analysis. *J Vasc Interv Radiol* 2017; **28**: 576–82.
- 19 Rassam F, Roos E, van Lienden KP, et al. Modern work-up and extended resection in perihilar cholangiocarcinoma: the AMC experience. *Langenbeck's Arch Surg* 2018; **403**: 289–307.
- 20 Jo JH, Chung MJ, Han DH, et al. Best options for preoperative biliary drainage in patients with Klatskin tumors. *Surg Endosc* 2017; **31**: 422–29.
- 21 Inamdar S, Slattery E, Bhalla R, Sejpal DV, Trindade AJ. Comparison of adverse events for endoscopic vs percutaneous biliary drainage in the treatment of malignant biliary tract obstruction in an inpatient national cohort. *JAMA Oncol* 2016; **2**: 112–17.
- 22 Otao R, Beppu T, Isiko T, et al. External biliary drainage and liver regeneration after major hepatectomy. *Br J Surg* 2012; **99**: 1569–74.
- 23 Suzuki H, Iyomasa S, Nimura Y, Yoshida S. Internal biliary drainage, unlike external drainage, does not suppress the regeneration of cholestatic rat liver after partial hepatectomy. *Hepatology* 1994; **20**: 1318–22.
- 24 van de Laarschot LF, Jansen PL, Schaap FG, Olde Damink SW. The role of bile salts in liver regeneration. *Hepatol Int* 2016; **10**: 733–40.
- 25 Kamiya S, Nagino M, Kanazawa H, et al. The value of bile replacement during external biliary drainage: an analysis of intestinal permeability, integrity, and microflora. *Ann Surg* 2004; **239**: 510–17.
- 26 Yoshida Y, Ajiki T, Ueno K, et al. Preoperative bile replacement improves immune function for jaundiced patients treated with external biliary drainage. *J Gastrointest Surg* 2014; **18**: 2095–104.
- 27 Scheufele F, Aichinger L, Jager C, et al. Effect of preoperative biliary drainage on bacterial flora in bile of patients with periampullary cancer. *Br J Surg* 2017; **104**: e182–88.
- 28 Coelen RJ, Ruys AT, Wiggers JK, et al. Development of a risk score to predict detection of metastasized or locally advanced perihilar cholangiocarcinoma at staging laparoscopy. *Ann Surg Oncol* 2016; **23**: 904–10.
- 29 Forbes SJ, Newsome PN. Liver regeneration—mechanisms and models to clinical application. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 473–85.
- 30 Liu HX, Keane R, Sheng L, Wan YJY. Implications of microbiota and bile acid in liver injury and regeneration. *J Hepatol* 2015; **63**: 1502–10.
- 31 Ribero D, Zimmiti G, Aloia TA, et al. Preoperative cholangitis and future liver remnant volume determine the risk of liver failure in patients undergoing resection for hilar cholangiocarcinoma. *J Am Coll Surg* 2016; **223**: 87–97.
- 32 Coelen RJ, Huiskens J, Olthof PB, et al. Compliance with evidence-based multidisciplinary guidelines on perihilar cholangiocarcinoma. *United Eur Gastroenterol J* 2017; **5**: 519–26.
- 33 Al-Kawas F, Aslanian H, Baillie J, et al. Percutaneous transhepatic vs. endoscopic retrograde biliary drainage for suspected malignant hilar obstruction: study protocol for a randomized controlled trial. *Trials* 2018; **19**: 108.