RISK ASSESSMENT AND PERIOPERATIVE CARE IN PERIHILAR CHOLANGIOCARCINOMA

ACADEMISCH PROEFSCHRIFT

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Chapter 1

Compliance to evidence-based multidisciplinary guidelines on perihilar cholangiocarcinoma

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United European Gastroenterology Journal 2016

Abstract

Background: Discrepancies are often noted between management of perihilar cholangiocarcinoma (PHC) in regional hospitals and the eventual treatment plan in specialized centers.

Objective: To evaluate whether regional centers adhere to guideline recommendations following implementation in 2013.

Methods: Data were analyzed from all consecutive patients with suspected PHC referred to our academic center between June 2013 and December 2015. Frequency and quality of biliary drainage and imaging at referring centers were assessed as well as the impact of inadequate initial drainage.

Results: Biliary drainage was attempted at regional centers in 83 of 158 patients (52.5%), with a technical and therapeutic success rate of 79.5% and 50%, respectively, and a complication rate of 45.8%. The computed tomography protocol was not in accordance with guidelines in 52.8% of referrals. In 45 patients (54.2%) who underwent drainage in regional centers, additional drainage procedures were required after referral. Initial inadequate biliary drainage at a regional center was significantly associated with more procedures and a prolonged waiting-time until surgery. A trend towards more drainage-related complications was observed among patients with inadequate initial drainage (54.7% vs. 39.0%, P = 0.061).

Conclusion: Despite available guidelines, suboptimal management of PHC persists in many regional centers and affects eventual treatment strategies.

Chapter 2

Preoperative endoscopic versus percutaneous transhepatic biliary drainage in potentially resectable perihilar cholangiocarcinoma (DRAINAGE trial): design and rationale of a randomized controlled trial

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BMC Gastroenterology 2015

Abstract

Background: Liver surgery in perihilar cholangiocarcinoma (PHC) is associated with high postoperative morbidity because the tumor typically causes biliary obstruction. Preoperative biliary drainage is used to create a safer environment prior to liver surgery, but biliary drainage may be harmful when severe drainage-related complications deteriorate the patients' condition or increase the risk of postoperative morbidity. Biliary drainage can cause cholangitis/cholecystitis, pancreatitis, hemorrhage, portal vein thrombosis, bowel wall perforation, or dehydration. Two methods of preoperative biliary drainage are mostly applied: endoscopic biliary drainage, which is currently used in most regional centers before referring patients for surgical treatment, and percutaneous transhepatic biliary drainage. Both methods are associated with severe drainage-related complications, but two small retrospective series found a lower incidence in the number of preoperative complications after percutaneous drainage compared to endoscopic drainage (18-25% versus 38-60%, respectively). The present study randomizes patients with potentially resectable PHC and biliary obstruction between preoperative endoscopic or percutaneous transhepatic biliary drainage.

Methods/Design: The study is a multi-center trial with an 'all-comers' design, randomizing patients between endoscopic or percutaneous transhepatic biliary drainage. All patients selected to potentially undergo a major liver resection for presumed PHC are eligible for inclusion in the study provided that the biliary system in the future liver remnant is obstructed (even if they underwent previous inadequate endoscopic drainage). Primary outcome measure is the total number of severe preoperative complications between randomization and exploratory laparotomy. The study is designed to detect superiority of percutaneous drainage: a provisional sample size of 106 patients is required to detect a relative decrease of 50% in the number of severe preoperative complications (alpha = 0.95; beta = 0.8). Interim analysis after inclusion of 53 patients (50%) will provide the definitive sample size. Secondary outcome measures encompass the success of biliary drainage, quality of life, and postoperative morbidity and mortality.

Discussion: The DRAINAGE-trial is designed to identify a difference in the number of severe drainage-related complications after endoscopic and percutaneous transhepatic biliary drainage in patients selected to undergo a major liver resection for perihilar cholangiocarcinoma.

Trial registration: Netherlands Trial Register (NTR4243, 11 October 2013)

Chapter 3

Percutaneous preoperative biliary drainage for resectable perihilar cholangiocarcinoma: no association with survival and no increase in seeding metastases

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Annals of Surgical Oncology 2015

Abstract

Background: Endoscopic biliary drainage (EBD) and percutaneous transhepatic biliary drainage (PTBD) are both used to resolve jaundice prior to surgery for perihilar cholangiocarcinoma (PHC). PTBD has been associated with seeding metastases. The aim of this study was to compare overall survival (OS), and the incidence of initial seeding metastases that potentially influence survival, in patients with preoperative PTBD versus EBD.

Methods: Between 1991 and 2012, 278 patients underwent preoperative biliary drainage and resection of PHC at two institutions (Netherlands and USA). Of these, 33 patients were excluded for postoperative mortality. Among the 245 included patients, 88 patients who underwent preoperative PTBD (with or without previous EBD) were compared with 157 patients who underwent EBD-only. Survival analysis was done with Kaplan-Meier and Cox regression with propensity score adjustment.

Results: Unadjusted median OS was comparable between the PTBD group (35 months) and EBD-only group (41 months; *P*=0.26). After adjustment for propensity score, OS between the PTBD group and EBD-only group was similar (hazard ratio, 1.05; 95% CI, 0.74-1.49; *P*=0.80). Seeding metastases in the laparotomy scar occurred as initial recurrence in 7 patients, including 3 patients (3.4%) in the PTBD group and 4 patients (2.7%) in the EBD-only group (*P*=0.71). No patient had an initial recurrence in percutaneous catheter tracts.

Conclusions: The present study found no effect of PTBD on survival compared to patients with EBD and no increase in seeding metastases that develop as initial recurrence. These data suggest that PTBD can safely be used in preoperative management of PHC.

Chapter 4

External biliary drainage following major liver resection for perihilar cholangiocarcinoma: impact on development of liver failure and biliary leakage

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HPB (Oxford) 2016

Abstract

Background: Preoperative biliary drainage is considered essential in perihilar cholangiocarcinoma (PHC) requiring major hepatectomy with biliary-enteric reconstruction. However, evidence for postoperative biliary drainage as to protect the anastomosis is currently lacking. This study investigated the impact of postoperative external biliary drainage on the development of post-hepatectomy biliary leakage and liver failure (PHLF).

Methods: All patients who underwent major liver resection for suspected PHC between 2000 and 2015 were retrospectively analyzed. Biliary leakage and PHLF were defined as grade B or higher according to the International Study Group of Liver Surgery criteria.

Results: Eighty-nine out of 125 (71%) patients had postoperative external biliary drainage. PHLF was more prevalent in the drain group (29% versus 6%; *P*=0.004). There was no difference in the incidence of biliary leakage (32% versus 36%). On multivariable analysis, postoperative external biliary drainage was identified as an independent risk factor for PHLF (Odds-ratio 10.3, 95% confidence interval 2.1-50.4; *P*=0.004).

Conclusions: External biliary drainage following major hepatectomy for PHC was associated with an increased incidence of PHLF. It is therefore not recommended to routinely use postoperative external biliary drainage, especially as there is no evidence that this decreases the risk of biliary anastomotic leakage.

Chapter 5

In vitro detection of cholangiocarcinoma cells using a fluorescent protein-expressing oncolytic herpes virus

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Submitted

Abstract

Background: Pathological confirmation is desired prior to high-risk surgery for suspected perihilar cholangiocarcinoma (PHC). Preoperative tissue diagnosis is limited by poor sensitivity of available techniques, resulting in an incidence of benign disease in resected specimens of up to 15%. In the last decade, the field of oncolytic viral therapy has found application in the detection of cancer cells, but these techniques have never been clinically validated for PHC. This study therefore aimed to validate whether a tumor-specific enhanced green fluorescent protein (eGFP)-expressing oncolytic virus could be used for cholangiocarcinoma cell detection.

Methods: Extrahepatic cholangiocarcinoma cell lines SK-ChA-1, EGI-1, TFK-1 and control cells, including primary human liver cells, were exposed to the oncolytic herpes simplex type 1 virus NV1066 for up to 24 hours in adherent culture. eGFP expression was measured by fluorescence-assisted cell sorting and mixtures of benign and cholangiocarcinoma cells were analyzed by imaging flow cytometry. The technique was validated for cells in suspension and cultured cells that had been exposed to crude patient bile.

Results: Optimal incubation time of cholangiocarcinoma cells with NV1066 was determined at 6 to 8 hours, yielding 15% eGFP-expressing cells at a multiplicity of infection of 0.1. Cells were able to survive 2-hour crude bile exposure and remained capable of producing eGFP following NV1066 infection. Detection of malignant cells was possible at the highest dilution tested (10 cancer cells among 2×10^5 normal liver cells), though hampered by non-target cell autofluorescence. The technique was not applicable to cells in suspension due to insufficient eGFP production.

Conclusion: A fraction of cholangiocarcinoma cells can be detected in vitro using an eGFP-expressing oncolytic virus and flow cytometry. However, clinical use requires this technique to be employed on cells in suspension. Accordingly, as yet the technique is not suitable for standardized clinical diagnostics in PHC.

Chapter 6

External validation of a clinically based staging system for perihilar cholangiocarcinoma

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Submitted

Abstract

Background: The Mayo Clinic recently presented a new staging system that is applicable to all patients with perihilar cholangiocarcinoma (PHC) regardless of subsequent treatment. The staging system assigns patients to one of four stages, depending on the patients' performance status, serum CA19-9 level, and radiological parameters including tumor size, suspected vascular involvement, and metastatic disease. We aimed to validate this staging system.

Methods: All consecutive patients with PHC who were evaluated and treated in two tertiary centers between January 2002 and December 2014 were identified. Baseline characteristics required for the prognostic model were collected from medical records and imaging parameters were reassessed by experienced abdominal radiologists. Overall survival (OS) was analyzed using the Kaplan-Meier method and comparison of staging groups was performed using the log-rank test and Cox proportional hazard regression analysis. Discriminative performance was quantified by the concordance (C)-index. Subgroup analysis was performed for treatment subgroups.

Results: A total of 600 patients were staged according to the Mayo Clinic model, allocating 23, 80, 357 and 140 patients to stages I, II, III and IV, respectively. Median OS was 11.6 months. Median OS of stages I, II, III and IV was 33.2, 19.7, 12.1 and 6.0 months, with hazard ratios (95% confidence interval) of 1.0 (reference), 2.02 (1.14-3.58), 2.71 (1.59-4.64) and 4.00 (2.30-6.95), respectively (P<0.001). The C-index (95% CI) was 0.59 (0.56-0.61) for the entire cohort. Statistically significant prognostic stratification was also observed in the laparotomy subgroup (P=0.011).

Conclusion: The Mayo Clinic staging system for patients with PHC demonstrated stratification in four stages that differed significantly in median survival. As the discriminative performance of the model was moderate, it may require improvement prior to clinical implementation.

Chapter 7

Diagnostic accuracy of staging laparoscopy for detecting metastasized or locally advanced perihilar cholangiocarcinoma: a systematic review and meta-analysis

R.J.S. Coelen, A.T. Ruys, M.G.H. Besselink, O.R.C. Busch, T.M. van Gulik

Surgical Endoscopy 2016

Abstract

Background: Despite extensive preoperative staging, still almost half of patients with potentially resectable perihilar cholangiocarcinoma (PHC) have locally advanced or metastasized disease upon exploratory laparotomy. The value of routine staging laparoscopy (SL) in these patients remains unclear with varying results reported in the literature. The aim of the present systematic review was to provide an overview of studies on SL in PHC and to define its current role in preoperative staging.

Methods: A systematic review and meta-analysis was performed in PubMed and EMBASE regarding studies providing data on the diagnostic accuracy of SL in PHC. Primary outcome measures were the overall yield and sensitivity to detect unresectable disease. Secondary outcomes were the yield and sensitivity for recent studies (after 2010) and large study cohorts (≥ 100 patients) and specific (metastatic) lesions. Methodological quality of studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.

Results: From 173 records, 12 studies including 832 patients met the inclusion criteria. The yield of SL in PHC varied from 6.4-45.0% with a pooled yield of 24.4% (95% Confidence Interval [CI]: 16.4-33.4). Sensitivity to detect unresectable disease ranged from 31.6-75% with a pooled sensitivity of 52.2% (95% CI: 47.1%-57.2%). Sensitivity was highest for peritoneal metastases (80.7%, 95% CI: 70.9-88.3). Subgroup analysis revealed that the yield and sensitivity tended to be lower for studies after 2010. Considerable heterogeneity was detected among the studies.

Conclusions: The results of the pooled analyses suggest that one in four patients with potentially resectable PHC benefit from SL. Given considerable heterogeneity, a trend to lower yield in more recent studies and further improvement of preoperative imaging over time, the routine use of SL seems discouraging. Studies that identify predictors of unresectability, that enable selection of patients who will benefit the most from this procedure, are needed.

Chapter 8

Development of a risk score to predict detection of metastasized or locally advanced perihilar cholangiocarcinoma at staging laparoscopy

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Annals of Surgical Oncology 2016

Abstract

Background: Nearly half of patients with perihilar cholangiocarcinoma (PHC) have incurable tumors at laparotomy. Staging laparoscopy (SL) potentially detects metastases or locally advanced disease, thereby avoiding unnecessary laparotomy. The diagnostic yield of SL, however, has decreased with improved imaging in recent years. The aim of this study was to identify predictors for detecting metastasized or locally advanced PHC at SL and to develop a risk score to select patients who may benefit most from this procedure.

Methods: Data of patients with potentially resectable PHC who underwent SL between 2000-2015 in our center were retrospectively analyzed. Multivariable logistic regression analysis was used to identify independent predictors and to develop a preoperative risk score.

Results: Unresectable PHC was detected in 41 of 273 patients undergoing SL (yield 15%). Overall sensitivity of SL was 30% with highest sensitivity to detect peritoneal metastases (73%). Preoperative imaging factors that were independently associated with unresectability at SL were tumor size ≥4.5 cm, bilateral portal vein involvement, suspected lymph node metastases and suspected (extra)hepatic metastases on imaging without the possibility for diagnosis by percutaneous- or endoscopic ultrasound-guided biopsy. The derived preoperative risk score showed good discrimination to predict unresectability (area under the curve, 0.77, 95% confidence interval 0.68-0.86) and identified three subgroups with a predicted low-risk of 7% (N=203 patients), intermediate-risk of 21% (N=39) and high-risk of 58% (N=31).

Conclusions: A selective approach for SL in PHC is recommended since the overall yield is low. The proposed preoperative risk score is useful in selecting patients for SL.

Chapter 9

Ablation with irreversible electroporation in patients with advanced perihilar cholangiocarcinoma (ALPACA): a multicenter phase I/II safety study protocol

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Submitted

Abstract

Background: The majority of patients with perihilar cholangiocarcinoma (PHC) has locally advanced disease or distant lymph node metastases upon presentation or exploratory laparotomy, which makes them not eligible for resection. As the prognosis of patients with locally advanced PHC or lymph node metastases in the palliative setting is significantly better compared to patients with organ metastases, ablative therapies may be beneficial. Unfortunately, current ablative options are limited. Photodynamic therapy causes skin phototoxicity and thermal ablative methods, such as stereotactic body radiation therapy and radiofrequency ablation, are affected by a heat/cold-sink effect when tumors are located close to vascular structures, such as the liver hilum. These limitations may be overcome by irreversible electroporation (IRE), a relatively new ablative method that is currently being studied in several other soft tissue tumors, such as hepatic and pancreatic tumors.

Methods/Design: In this multicenter phase I/II safety and feasibility study, 20 patients with unresectable PHC due to vascular or distant lymph node involvement will undergo IRE. Ten patients who present with unresectable PHC will undergo computed tomography (CT) guided percutaneous IRE, whereas ultrasound-guided IRE will be performed in 10 patients with unresectable tumors detected at exploratory laparotomy. The primary outcome is the total number of clinically relevant complications (Common Terminology Criteria for Adverse Events [CTCAE], score of ≥ 3) within 90 days. Secondary outcomes are the success rate of completing IRE, intra-procedural complications, hospital stay, quality of life, tumor response on CT imaging, blood biomarker response, time between IRE and start of palliative chemotherapy, metal stent patency, and progression-free and overall survival (OS). Follow-up will be 2 years.

Discussion: The ALPACA study is designed to assess safety and feasibility of IRE for advanced PHC. Potential benefits may be prolonged metal stent patency rate and increased survival.

Trial registration: Netherlands Trial Register [NTR5948, 4 July 2016]. Dutch Central Committee on Research Involving Human Subjects registration number NL56231.018.15.

Chapter 10

Complications after surgery for perihilar cholangiocarcinoma

E. Roos, R.J.S. Coelen, T.M. van Gulik

Appearing as a book chapter in 'Complications after GI Surgery'. Dr. Nundy & Prof. Gouma (Ed.)

Abstract

Cholangiocarcinoma is a heterogeneous group of malignancies that originates from the biliary tract. Perihilar cholangiocarcinoma is the most frequent form and represents 50-70% of all bile duct tumors. The majority of patients present with unresectable tumors at the time of diagnosis and, ultimately, only 20% of all patients are eligible to undergo curative resection. Partial hepatectomy with concomitant extrahepatic bile duct resection is the preferred treatment to achieve tumor-free margins, but this aggressive and technically challenging approach is associated with severe morbidity. This chapter deals with the specific operative risks and postoperative complications that frequently occur after resection of perihilar cholangiocarcinoma. Strategies for the management of these events are provided. Tailored preoperative care is the key to lowering the risk of postoperative complications.

Chapter 11

Preoperative computed tomography assessment of skeletal muscle mass is valuable in predicting outcomes following hepatectomy for perihilar cholangiocarcinoma

R.J.S. Coelen, J.K. Wiggers, C.Y. Nio, M.G.H. Besselink, O.R.C. Busch, D.J. Gouma, T.M. van Gulik

HPB (Oxford) 2015

Abstract

Background: Liver surgery for perihilar cholangiocarcinoma (PHC) is associated with high rates of morbidity and mortality.

Objectives: This study investigated the impact of low skeletal muscle mass on short- and longterm outcomes following hepatectomy for PHC.

Methods: Patients included underwent liver surgery for PHC between 1998 and 2013. Total skeletal muscle mass was measured at the level of the third lumbar vertebra using available preoperative computed tomography images. Sex-specific cut-offs for low skeletal muscle mass were determined by optimal stratification.

Results: In 100 patients, low skeletal muscle mass was present in 42 (42.0%) subjects. The rate of postoperative complications (Clavien–Dindo Grade III and higher) was greater in patients with low skeletal muscle mass (66.7% versus 48.3%; multivariable adjusted $P = 0.070$). Incidences of sepsis (28.6% versus 5.2%) and liver failure (35.7% versus 15.5%) were increased in patients with low skeletal muscle mass. In addition, 90-day mortality was associated with low skeletal muscle mass in univariate analysis (28.6% versus 8.6%; $P = 0.009$). Median overall survival was shorter in patients with low muscle mass (22.8 months versus 47.5 months; $P = 0.014$). On multivariable analysis, low skeletal muscle mass remained a significant prognostic factor (hazard ratio 2.02; $P = 0.020$).

Conclusions: Low skeletal muscle mass has a negative impact on postoperative mortality and overall survival following resection of PHC and should therefore be considered in preoperative risk assessment.

Chapter 12

External validation of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) risk model to predict operative risk in perihilar cholangiocarcinoma

R.J.S. Coelen*, P.B. Olthof*, S. van Dieren, M.G.H. Besselink, O.R.C. Busch, T.M. van Gulik
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JAMA Surgery 2016

Abstract

Importance: Resection of perihilar cholangiocarcinoma (PHC) is high-risk surgery, with reported operative mortality up to 17%. Therefore, preoperative risk assessment is needed to identify high-risk patients and anticipate postoperative adverse outcomes.

Objective: To provide external validation of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) risk model in a Western cohort of PHC.

Design, setting, and participants: E-PASS variables were collected from a database including 156 consecutive patients who underwent resection for suspected PHC between January 1, 2000, and December 31, 2015, at the Academic Medical Center, Amsterdam, the Netherlands. The accuracy of E-PASS using intra-operative variables and its modified form that can be used before surgery (mE-PASS) in predicting mortality was assessed by area under the curve (AUC) analysis (discrimination) and by the Hosmer-Lemeshow goodness-of-fit test (calibration).

Main outcomes and measures: In-hospital mortality, severe morbidity (Clavien-Dindo Grade ≥III) and high Comprehensive Complication Index.

Results: Among 156 patients included in the study, the median age was 63 years, and 62.8% (n = 98) were male. Of them, 85.3% (n = 133) underwent major liver resection. Severe morbidity occurred in 51.3% (n = 80), and in-hospital mortality was 13.5% (n = 21). Both E-PASS and mE-PASS had adequate discriminative performance, with areas under the curve of 0.78 (95% CI, 0.67-0.88) and 0.79 (95% CI, 0.70-0.89), respectively, while E-PASS showed better calibration (P = 0.33 vs P = 0.02, Hosmer-Lemeshow goodness-of-fit test). The ratios of observed to expected mortality were 1.31 for E-PASS and 1.24 for mE-PASS. Both models were able to distinguish groups with low risk, intermediate risk, and high risk, with observed mortality rates of 0.0% to 3.6%, 8.3% to 9.0%, and 25.0% to 28.3%, respectively. Severe morbidity and a high Comprehensive Complication Index were more frequently observed among high-risk patients.

Conclusions and relevance: Both E-PASS models accurately identify patients at high risk of postoperative in-hospital mortality after resection for PHC. The mE-PASS model can be used before surgery in outpatient settings and allows for risk assessment and shared decision making.

Chapter 13

^{99m}Tc-mebrofenin hepatobiliary scintigraphy predicts liver failure following major liver resection for perihilar cholangiocarcinoma

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Submitted

Abstract

Background: Posthepatectomy liver failure (PHLF) is a threatening complication after liver surgery, especially in perihilar cholangiocarcinoma (PHC). This study aimed to assess the value of preoperative assessment of liver function using ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS) to predict PHLF in comparison with liver volume in PHC patients.

Methods: All patients who underwent resection of suspected PHC in a single center between 2000 and 2015 were included in the analysis. PHLF was graded according to the International Study Group of Liver Surgery criteria with grade B/C considered clinically relevant. A cut-off value for the prediction of PHLF was calculated using the receiver operating characteristic curve analysis.

Results: A total of 116 patients were included of which 27 (23%) suffered of PHLF. Area under the curve values for the prediction of PHLF were 0.74 (95%CI 0.63-0.86) for FLR function and 0.63 (95%CI 0.47-0.80) for FLR volume. A cut-off for liver function was set at 8.5%/min, which resulted in a negative predictive value of 94% and positive predictive value of 41%.

Conclusion: Assessment of liver function with HBS had better predictive value for PHLF than liver volume in patients undergoing major liver resection for suspected PHC. The cut-off of 8.5%/min can help to select patients for portal vein embolization.

Summary and future perspectives

Perihilar cholangiocarcinoma (PHC), also known as 'Klatskin' tumor, is a rare form of cancer that arises at or near the biliary confluence. Each year approximately 200 patients are newly diagnosed in the Netherlands. Many pitfalls are encountered at various stages of the management of PHC, making it one of the most complex gastrointestinal malignancies. Due to the frequent occurrence of metastases or locally advanced tumors, only 10 to 20% of patients are ultimately eligible for surgical resection. Liver resection with combined extrahepatic bile duct resection remains the only potential chance of long term survival, but is technically challenging and not without risks. The aggressive surgical approach that is necessary to aim for tumor-free margins is associated with a high probability of complications and postoperative mortality. The aim of this thesis was to provide recommendations for the staging of PHC, risk assessment, and perioperative care in order to contribute to the improvement of patient selection and surgical safety.

Part 1 – Pre- and postoperative biliary drainage

Jaundice is the most common manifestation of PHC and is relieved with biliary drainage. Drainage of obstructed bile ducts is an important step in the management of PHC and needs to be tailored to the eventual treatment plan. Recent, national clinical guidelines have provided recommendations for the work-up of these patients in regional hospitals prior to referral to a tertiary center. It is recommended that biliary drainage is not attempted in centers that have limited expertise with endoscopic and percutaneous biliary drainage. In **chapter 1**, we evaluated whether regional hospitals adhere to the recommendations in these guidelines. Among 158 patients who were referred to the Academic Medical Center (AMC) within a two-and-a-half-year period after guideline implementation, biliary drainage was attempted at regional centers in 83 patients (53%). The technical and therapeutic success rates were only 80% and 50%, respectively. Almost half of patients underwent two or more drainage procedures. Half of the patients that underwent drainage in regional centers required additional drainage in the AMC, mainly because of stent dysfunction or inadequate drainage of the future liver remnant. We found that initial inadequate biliary drainage at a regional center was associated with a higher number of drainage procedures, a prolonged waiting-time until surgery, and a trend towards more drainage-related complications. We also observed that the computed tomography protocol was not in accordance with guidelines in half of referrals and necessitated additional imaging at our center in order to enable adequate staging of the tumors. The observed discrepancy between the work-up in regional centers and eventual treatment strategy in our tertiary center has led to the development of a national multidisciplinary clinical pathway that aims to further optimize patient care.

The following chapters in the first part of the thesis focused on the technique of biliary drainage in PHC. In **chapter 2**, a protocol is presented for a multicenter, randomized controlled trial (DRAINAGE trial) comparing endoscopic and percutaneous biliary drainage in patients selected to undergo major liver resection for PHC. This trial is designed to investigate whether a percutaneous transhepatic approach is superior with regard to the total number of severe drainage-related complications between time of

randomization and exploratory laparotomy. A provisional sample size of 106 patients is required to detect a relative decrease of 50% in the number of severe preoperative complications. Secondary outcome measures are the success of biliary drainage, quality of life, and postoperative morbidity and mortality.

Recent studies from Eastern centers have reported an increased risk of seeding metastases after preoperative percutaneous transhepatic biliary drainage and resection. On the basis of these findings, many centers from Asia have recently suggested that endoscopic drainage should be preferred. However, from an oncologic perspective, only recurrences that affect overall survival are considered clinically relevant. Therefore, a retrospective analysis of the long-term outcomes of preoperative endoscopic (N=157) and percutaneous biliary drainage (N=88) in two Western centers was performed in **chapter 3**. The number of seeding metastases occurring in the laparotomy scar was similar between the two groups (3% in both groups). No patient had an initial recurrence in percutaneous catheter tracts. After adjustment for propensity score to account for potential confounders, overall survival between the endoscopically and percutaneously drained group was similar. The data from this study suggest that percutaneous drainage can safely be used in the preoperative management. The decision to use this approach should not be influenced by concerns about catheter tract recurrences as they are very rare and probably do not affect overall survival.

Chapter 4 further elaborates on the use of percutaneous biliary drains. These drains are often left in situ during resection of PHC as they are thought to protect the biliary-enteric anastomosis from dehiscence and leakage after surgery. We analyzed the protective effect of these trans-anastomotic drains and the impact of external biliary drainage on development of liver failure after resection. Among 125 patients that underwent resection, 89 (71%) patients had a postoperative trans-anastomotic external biliary drain, while the remaining patients had no such drain. The occurrence of liver failure was higher in the drain group (29% versus 6%), while the incidence of biliary leakage was similar between the groups (32% versus 36%). On multivariable analysis, postoperative external biliary drainage was identified as an independent risk factor for liver failure (odds ratio 10.3). These findings question the assumed protective effect of postoperative external biliary drains on the integrity of the biliary-enteric anastomosis. Given the increased risk of liver failure, the routine use of such drains is not recommended. However, when external biliary drains are considered indicated in patients with multiple, high-risk biliary anastomosis, bile acid replacement therapy should be considered as bile acids have recently been identified as mediators of liver regeneration.

Part 2 – Preoperative staging

The second part of the thesis discusses the limitations and potential improvements of preoperative staging. Due to poor sensitivity of available techniques to obtain histological or cytological proof of malignancy, many patients are operated on without confirmed diagnosis. Ultimately, up to 15% of patients who undergo resection on the suspicion of PHC appear to have a benign lesion. In **chapter 5**, we performed an experimental study to examine whether the tumor-specific oncolytic virus NV1066

could be used for cholangiocarcinoma cell detection. NV1066 is a modified herpes simplex type 1 virus that expresses an enhanced green fluorescent protein (eGFP) upon infection and replication in tumor cells. In several in-vitro experiments, cholangiocarcinoma cell lines were exposed to NV1066 for up to 24 hours. Expression of eGFP was measured by fluorescence-assisted cell sorting and indicated the detection of cancer cells. We found that the optimal incubation time of cholangiocarcinoma cells with NV1066 was determined at 6 to 8 hours, but yielded only 15% eGFP-expressing cells. To simulate the clinical situation, where circulating cholangiocarcinoma cells in bile are obtained during biliary drainage, we investigated the toxic effect of bile on these cell lines. Cells were able to survive 2-hour crude bile exposure and remained capable of producing eGFP following NV1066 incubation. Detection of malignant cells was possible at a dilution of 10 cholangiocarcinoma cells among 2×10^5 normal liver cells, though was hampered by non-target cell autofluorescence. The technique was not applicable to cells in suspension due to insufficient eGFP production. These results therefore suggest that the NV1066 technique is not suitable for standardized clinical diagnostics in PHC.

Chapter 6 describes the external validation of a new staging system from the Mayo Clinic, that is applicable to all patients with PHC regardless of subsequent treatment. The staging system assigns patients to one of four stages, depending on the patients' performance status, serum CA19-9 level, and radiological parameters including tumor size, suspected vascular involvement, and metastatic disease. We were able to apply this staging system to a cohort of 600 patients from two specialized centers. Median overall survival of stages I, II, III and IV was 33, 20, 12 and 6 months, with hazard ratios of 1.0 (reference), 2.0, 2.7 and 4.0, respectively. The model may thus be valuable to use for informing patients about prognosis and may aid in the stratification of patients for clinical trials. However, since the discriminative performance was moderate, as indicated by a concordance index of 0.59, the model may require some improvement prior to clinical implementation.

The high incidence of locally advanced tumors and occult metastases encountered upon exploratory laparotomy have led us to investigate the use of staging laparoscopy in addition to standard imaging. **Chapter 7** presents a systematic review and meta-analysis of the diagnostic accuracy of staging laparoscopy for detecting metastasized or locally advanced tumors. We found 12 studies including 832 patients. The yield, which represents the number of patients (expressed as a percentage of all patients that undergo staging laparoscopy) that are withheld from an unnecessary laparotomy, ranged from 6 to 45% with a pooled estimate of 24%. The pooled sensitivity to detect unresectable disease was 52% and sensitivity was highest for peritoneal metastases (81%). The results of our meta-analysis suggest that one in four patients with potentially resectable PHC benefit from staging laparoscopy. However, given considerable heterogeneity among the studies, a trend towards lower yield in more recent series and further improvement of preoperative imaging over time, the routine use of staging laparoscopy seems not to be recommended.

Following the results of the previous chapter and experience from our own clinical practice, a risk score was developed in **chapter 8** that allows selection of patients who may benefit most from staging

laparoscopy. Staging laparoscopy was performed in 273 patients and revealed metastatic or locally advanced disease in 41 patients (yield 15%). Four independent preoperative predictors were found: tumor size ≥4.5 cm, bilateral portal vein involvement, suspected lymph node metastases or suspected (extra)hepatic metastases on imaging without the possibility for diagnosis by percutaneous- or endoscopic ultrasound-guided biopsy. The derived risk score had good predictive accuracy and identified three subgroups with a predicted low-risk of 7%, intermediate-risk of 21% and high-risk of 58%. These results support a selective approach to staging laparoscopy using the proposed risk score in patients with potentially resectable PHC.

The fact that the majority (80%) of patients are not eligible for curative resection has stimulated us to explore the role of local ablation therapies in addition to systemic chemotherapy. **Chapter 9** describes the protocol for a multicenter phase I/II study (ALPACA) that investigates the safety and feasibility of irreversible electroporation in patients with advanced PHC. Irreversible electroporation (NanoKnife) is an image-guided ablation technique based on the creation of short-pulsed, high-voltage current fields that permeabilize the cellular membrane, resulting in the disruption of intracellular homeostasis and controlled cell death. The ALPACA study will include 20 patients with unresectable PHC due to vascular or distant lymph node involvement. Ten patients who present with advanced tumors will be treated through a CT-guided percutaneous approach, whereas 10 patients with unresectable PHC at laparotomy will undergo ultrasound-guided open irreversible electroporation. The primary outcome is the total number of clinically relevant complications within 90 days. Secondary outcomes include quality of life, tumor response, metal stent patency and survival.

Part 3 – Perioperative risk assessment

The final part of the thesis deals with the preoperative assessment of the risks associated with surgical resection. More than 50% of patients develop severe complications and even in experienced centers, 90-day mortality rates range from 5 to 17%. **Chapter 10** provides an overview of the most common and also most dreaded complications associated with resection of PHC. The causes of liver failure, biliary leakage, hemorrhage, multi organ failure and infections are discussed and strategies for the management of these events are provided.

The frailty status of patients may be reflected by the loss of skeletal muscle mass, a phenomenon that is also known as sarcopenia. **Chapter 11** investigated the impact of low skeletal muscle mass, as measured on computed tomography images, on short- and long-term outcomes after major liver resection for PHC. This study showed that the rate of postoperative complications was greater in patients with low skeletal muscle mass (67% versus 48%). Importantly, high postoperative mortality was observed in these patients (29%) when compared to patients with normal muscle mass (9%). Furthermore, low skeletal muscle mass was identified as a poor prognostic factor for overall survival after resection (hazard ratio 2.0). Measurement of skeletal muscle mass could thus be valuable in preoperative risk assessment, and amplification of muscle mass using nutritional intervention or exercise may potentially improve postoperative outcomes.

Chapter 12 explores a more comprehensive risk model to predict complications and mortality after surgery. The Estimation of Physiologic Ability and Surgical Stress (E-PASS) model, that was originally developed in Japan, incorporates both patient-related factors as well as surgical stress parameters. The modified preoperative version (mE-PASS) is clinically valuable at the time of surgical planning, as the number of surgical variables are reduced and fixed stress scores are allocated to specific surgical procedures. Both models accurately identified patients at high risk of in-hospital mortality after resection of PHC and they were able to distinguish groups with low (0 to 4%), intermediate (8 to 9%), and high (25 to 28%) mortality risk. Severe complications were significantly more frequently observed among high-risk patients. The E-PASS and mE-PASS models could thus be used in risk assessment and shared decision making.

The risk of liver failure after major resection is most commonly assessed preoperatively by performing liver volumetry on computed tomography scans. However, as liver volume alone does not necessarily reflect liver function, **chapter 13** aimed to predict the risk of posthepatectomy liver failure by assessment of liver function. Liver function was measured preoperatively using ^{99m}Tc-mebrofenin hepatobiliary scintigraphy. This technique measures the hepatocyte uptake- and excretion rate of the radiopharmaceutical agent ^{99m}Tc-mebrofenin. In a cohort of 116 patients who underwent major liver resection for PHC, liver failure occurred in 23% of patients. Assessment of liver function using hepatobiliary scintigraphy had better predictive value for liver failure than liver volumetry. A cut-off for liver function at 8.5%/min resulted in a negative predictive value of 94%, indicating a very low risk of liver failure for a test result above the cut-off. Portal vein embolization may be considered in patients with lower liver function as calculated by hepatobiliary scintigraphy.

Future perspectives

This thesis addressed several pitfalls in the management of perihilar cholangiocarcinoma (PHC). Results from our analyses and recent publications have stressed the ongoing need for prospective studies. An important topic remains the improvement of preoperative diagnosis. As the technique consisting of the use of an oncolytic virus was found not suitable for clinical diagnostics, studies are desired to improve currently available techniques or develop new sensitive tests. Hopefully, we may expect more results from the promising Spyglass technique, a single-operator cholangioscopy system, for the evaluation of indeterminate biliary strictures.[1] Recently, a new diagnostic test was presented that showed high accuracy to distinguish immunoglobulin G4-associated cholangitis from biliary cancer by measuring the IgG4/IgG RNA ratio in serum.[2] This qPCR test will be prospectively evaluated in clinical practice in the coming years. Another emerging technique that has the potential to be of diagnostic value, is the detection of circulating tumor DNA in blood. Circulating tumor DNA is derived from tumor deposits and lysis of tumor cells and its presence has been demonstrated in other gastrointestinal malignancies.[3] Future studies will investigate the presence of circulating tumor DNA in so-called 'liquid' biopsies of patients with cholangiocarcinoma.

The design and carrying out of the DRAINAGE trial comparing endoscopic with percutaneous preoperative biliary drainage has resulted in a national collaboration between tertiary referral centers on cholangiocarcinoma research. We will certainly see subsequent studies on the management of PHC in the near future as many issues concerning biliary drainage remain to be elucidated. Several retrospective studies have recently shown that selected jaundiced patients, who require resection of less than 50% of the liver volume, do not benefit from preoperative biliary drainage in terms of safer surgery.[4-6] This finding requires confirmation within a prospective cohort study as a randomized controlled trial may not be feasible given the required sample size. Another question that may be resolved is whether in the palliative setting, the endoscopic or percutaneous route should be used for biliary drainage.

This thesis also discussed the observed discrepancy between the work-up in regional centers and eventual treatment strategies in tertiary hospitals, despite available (inter-)national guidelines. To improve the complex care of patients with PHC, a multidisciplinary clinical pathway was recently developed in collaboration with several tertiary hospitals and the Dutch Association of Comprehensive Cancer Centers.[7] This clinical pathway stimulates early communication between physicians and early referral of patients to specialized centers. Implementation of this clinical pathway has started in 2016.

Newly developed risk models and staging systems allow physicians to inform patients about their prognosis.[5, 8, 9] In this thesis, several risk models and risk factors were studied that may aid in patient selection for surgery. The newly proposed cut-off value for adequate liver function, as calculated with ^{99m}Tc-mebrofenin hepatobiliary scintigraphy, will lead to more portal vein embolization procedures prior to major liver resection for PHC in our center. This might constitute an important change in policy in

order to reduce postoperative mortality. Furthermore, the identification of low skeletal muscle mass as predictor of postoperative outcomes in liver surgery stress the need for studies on the effect of physical prehabilitation. A recent randomized study demonstrated that a 4-week prehabilitation program improved preoperative cardiopulmonary exercise tests prior to liver surgery.[10] However, future studies should investigate whether such programs, including nutritional intervention and physical exercise, improve muscle mass and muscle quality and subsequently, reduce surgical complications. To widely apply the risk models from this thesis, it is essential that our proposed risk score for staging laparoscopy, the use of hepatobiliary scintigraphy as predictor of liver failure, and the sex-specific cut-off values for defining low skeletal muscle mass are assessed in patient cohorts from other centers.

New ablative techniques are being investigated in patients with locally advanced PHC who are not eligible for surgical resection. The ALPACA study (Netherlands trial register number: NTR5948) will assess the safety and feasibility of irreversible electroporation (NanoKnife) in addition to systemic chemotherapy. The study is estimated to be completed in 2019. When this technique is considered to be suitable for patients with unresectable PHC, it is likely that randomized trials will be conducted to compare its potential survival benefit with modalities such as photodynamic therapy, endoscopic radiofrequency ablation, stereotactic body radiation therapy, and chemotherapy alone.

Adjuvant treatment for cholangiocarcinoma is currently receiving much attention. The poor prognosis of lymph node metastases and the high recurrence rate during follow-up of PHC emphasize the need for such therapies.[11] Although adjuvant chemotherapy has shown a survival benefit in other gastrointestinal malignancies such as high-risk or lymph node positive colorectal cancer, clinical trials for patients with cholangiocarcinoma have only recently been designed. The Netherlands is currently participating in the ACTICCA-1 trial (clinicaltrials.gov identifier: NCT02170090). This is a prospective randomized controlled phase III trial that assesses the clinical performance of gemcitabine with cisplatin versus observation alone in patients after resection of biliary cancer. The study is estimated to be completed in three years. Other chemotherapy regimens that are being studied in phase III trials include capecitabine monotherapy and the combination of gemcitabine and oxaliplatin (NCT00363584, NCT01313377). While results of prospective studies are to be awaited, recent publications of retrospective analyses have shown a benefit of adjuvant chemotherapy or chemoradiation on survival after resection of PHC.[12-14]

Mutational profiling of circulating tumor DNA or the (resected) tumor itself may allow targeted therapy and improve survival. Several targetable cholangiocarcinoma signaling pathways have been identified and include the epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and mitogen-activated protein kinase (MEK). Molecular inhibitors of these signaling networks are currently being studied and may provide more insight into the value of individualized therapy in the near future.[15, 16] Given the rarity and molecular complexity of the disease, an international collaboration is essential to stimulate scientific progress. An important step was made in 2015, when the European Network for the Study of Cholangiocarcinoma was created.[17] Future studies in this network will focus on

translational work to fill the gap between basic science and clinical studies. Hopefully, we will see progress in the identification of biomarkers specific for PHC, as these are needed for early diagnosis, prognosis and targeted therapies.

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List of publications

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1. Coelen RJ*, Olthof PB*, van Dieren S, Besselink MG, Busch OR, van Gulik TM. External validation of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) risk model to predict operative risk in perihilar cholangiocarcinoma. *JAMA Surg.* 2016 Aug 31 (Epub ahead of print)

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PhD portfolio

Name PhD student: Robert-Jan Coelen
PhD period: October 2013 – September 2016
Name PhD supervisor: Prof. dr. T.M. van Gulik

PhD training	Year	Workload (ECTS)
General courses		
BROK (Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers)	2013	0.9
Basic Laboratory Safety	2014	0.4
Clinical Data Management	2014	0.2
Clinical Epidemiology	2014	0.6
Crash course (bio)chemistry and biology	2014	0.4
Practical Biostatistics	2014	1.1
Project management	2014	0.6
AMC World of Science	2014	0.7
Specific courses		
Computing in R	2014	0.4
Laboratory animals (art. 9)	2014	3.9
Advanced Topics in Biostatistics	2015	2.1
Clinical Epidemiology 1: Randomized Clinical Trials	2015	0.9
Clinical Epidemiology 3: Evaluation of Medical Tests	2014	0.9
Clinical Epidemiology 4: Systematic Reviews	2014	0.7
Seminars, workshops and master classes		
Weekly department seminars	2013-2016	3.0
Master class perihilar cholangiocarcinoma AMC	2015	0.2
One day on liver surgery symposia AMC	2014, 2016	1.5
Teaching		
Mentoring/supervising of students		4.5
M.J. de Keijzer, master student, detection of cholangiocarcinoma cells using an oncolytic virus	2015-2016	2.0
B.V. van Rosmalen, bachelor student, systematic review of transarterial embolization of hepatocellular adenomas	2015-2016	1.0
T.A. Labeur, master student, validation of a staging system for perihilar cholangiocarcinoma	2015-2016	1.5
Grants, awards and prizes		
Travel Grant United European Gastroenterology Week	2015	
Best Clinical Research Award European Society for Surgical Research	2014	
Prof. dr. P.J. Klopperprijs	2014	
WBSO	2014-2016	
Other		
Country representative European Society for Surgical Research	2015-2016	2.0
Reviewer for journals	2014-2016	1.0

Development and implementation of a multidisciplinary clinical pathway for patients with suspicion of perihilar cholangiocarcinoma	2015-2016	2.0
Journal club	2013-2016	1.0
GUT club	2013-2016	1.0
Oral presentations		
Negative impact of sarcopenia on outcomes following hepatectomy for perihilar cholangiocarcinoma		
European Society for Surgical Research (ESSR), Budapest, Hungary	2014	0.5
Diagnosis and management of perihilar cholangiocarcinoma: experimental and clinical studies		
Surgical Research Society of Southern Africa (SRS-SA), Bloemfontein, South Africa	2015	0.5
Voorspellers van irresectabiliteit bij stageringslaparoscopie bij 265 patiënten met verdenking op een perihilair cholangiocarcinoom		
Chirurgendagen, Veldhoven	2015	0.5
A plea for selective use of staging laparoscopy for potentially resectable perihilar cholangiocarcinoma: an analysis of 273 patients		
United European Gastroenterology Week (UEGW), Barcelona, Spain	2015	0.5
Dutch Highlights at European-African Hepato-Pancreato-Biliary Association (EAHPBA), Zeist	2015	0.5
In vitro detection of cholangiocarcinoma cells using a fluorescent protein-expressing oncolytic herpes virus		
Symposium Experimenteel Onderzoek Heelkundige Specialismen (SEOHS), Leiden	2015	0.5
European Society for Surgical Research (ESSR), Prague, Czech Republic	2016	0.5
IgG4-associated cholangitis in patients resected for presumed perihilar cholangiocarcinoma		
European Society for Surgical Research (ESSR), Prague, Czech Republic	2016	0.5
NVGE najaarsvergadering, Veldhoven	2016	0.5
Referral of patients with suspicion of perihilar cholangiocarcinoma to a tertiary center: a retrospective audit following introduction of a national and international guideline		
International Hepato-Pancreato-Biliary Association (IHPBA), São Paulo, Brazil	2016	0.5
NVGE voorjaarsvergadering, Veldhoven	2016	0.5
Staging laparoscopy for detecting unresectable disease in patients with potentially resectable perihilar cholangiocarcinoma: a systematic review and meta-analysis		
International Hepato-Pancreato-Biliary Association (IHPBA), São Paulo, Brazil	2016	0.5
Development of a risk score to predict detection of metastasized or locally advanced perihilar cholangiocarcinoma at staging laparoscopy		
International Hepato-Pancreato-Biliary Association (IHPBA), São Paulo, Brazil	2016	0.5
External validation of a clinically based staging system for perihilar cholangiocarcinoma		

United European Gastroenterology Week (UEGW), Vienna, Austria	2016	0.5
NVGE najaarsvergadering, Veldhoven	2016	0.5
Poster presentations		
Preoperative skeletal muscle loss predicts outcomes following hepatectomy for perihilar cholangiocarcinoma		
United European Gastroenterology Week (UEGW), Vienna, Austria	2014	0.5
Symposium Experimenteel Onderzoek Heelkundige Specialismen (SEOHS), Groningen	2014	0.5
Percutaneous preoperative biliary drainage for resectable perihilar cholangiocarcinoma: no association with survival and no increase in seeding metastases		
United European Gastroenterology Week (UEGW), Barcelona, Spanje.	2015	0.5
Predictors of unresectable disease at staging laparoscopy in 265 patients with suspected perihilar cholangiocarcinoma		
European-African Hepato-Pancreato-Biliary Association (EAHPBA), Manchester, United Kingdom	2015	0.5
Oncological outcomes of liver resection for intrahepatic and perihilar cholangiocarcinoma: a Western European single centre experience		
European-African Hepato-Pancreato-Biliary Association (EAHPBA), Manchester, United Kingdom	2015	0.5
Preoperative endoscopic versus percutaneous transhepatic biliary drainage in potentially resectable perihilar cholangiocarcinoma: design and rationale of a randomized controlled trial		
International Hepato-Pancreato-Biliary Association (IHPBA), São Paulo, Brazil	2016	0.5
Scientific conferences		
SEOHS 2013, Maastricht	2013	0.25
SEOHS 2014, Groningen	2014	0.25
SEOHS 2015, Leiden	2015	0.25
Chirurgendagen 2015, Veldhoven	2015	0.25
Chirurgendagen 2016, Veldhoven	2016	0.25
NVGE voorjaarsvergadering 2016, Veldhoven	2016	0.5
NVGE najaarsvergadering 2016, Veldhoven	2016	0.25
EAHPBA 2015, Manchester, United Kingdom	2015	0.75
IHPBA 2016, São Paulo, Brazil	2016	0.75
UEGW 2015, Barcelona, Spain	2015	0.75
UEGW 2016, Vienna, Austria	2016	0.75
ESSR 2014, Budapest, Hungary	2014	0.75
ESSR 2016, Prague, Czech Republic	2016	0.75
SRS-SA 2015, Bloemfontein, South Africa	2015	0.5

Curriculum vitae

Robert-Jan Coelen (1987, Eindhoven) is a medical school graduate from Maastricht University and followed his PhD training at the department of surgery at the Academic Medical Center in Amsterdam.

After attending Gymnasium at the Van Maerlantlyceum in Eindhoven and Christelijk Lyceum Zeist, Robert-Jan finished the first year of Biomedical Sciences at Utrecht University. He then entered the medical faculty at Maastricht University where he combined the curricular courses with an honors scientific research program. Robert-Jan was involved in many studies in the field of hepatobiliary disease at the department of surgery at Maastricht University Medical Center (prof. dr. C.H.C. Dejong, dr. J.H.M.B. Stoot). As a medical student, he managed to publish several articles and present at international congresses. During medical training, he also spent several months in Nepal and Indonesia for clinical rotations.

After obtaining his medical degree in 2012, Robert-Jan worked as a resident (ANIOS) for 1 year at the department of surgery at Orbis Medical Center in Sittard (dr. A.G.M. Hoofwijk). He then took the opportunity to pursue his research in the field of hepatobiliary surgery at the Academic Medical Center in Amsterdam under supervision of prof. dr. T.M. van Gulik. During his PhD training, he studied the multidisciplinary management of perihilar cholangiocarcinoma and he was involved in the development and implementation of a clinical pathway for these patients. Robert-Jan was awarded several prizes including the prof. dr. P.J. Klopperpijs (2014). Currently, he is also representing his country in the European Society for Surgical Research and is a member of the organizing committee for their 2017 congress in Amsterdam.

In January 2017, he will start his surgical training at the VU Medical Center program (Prof. dr. D.L. van der Peet). Robert-Jan lives in Amsterdam and likes road cycling and playing tennis in his spare time.