



Samenvatting van het proefschrift

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"Tailored care in resectable Perihilar Cholangiocarcinoma"

Promotiedatum: 20 november 2015

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Surgical resection of perihilar cholangiocarcinoma offers a distinct benefit in long-term survival, but it is a complex procedure. The tumour may cause jaundice, extend into segmental branches of the bile ducts, or involve the portal vein and/or hepatic artery. Selecting the optimal treatment in patients with perihilar cholangiocarcinoma is a trade-off between opportunities for long-term survival against the danger of procedural risks: surgery offers a chance for long-term survival or cure, but perioperative complications may cause abrupt death.

Biliary drainage is often used to treat jaundice prior to surgery: it reduces the risk of postoperative complications such as liver failure and systemic infection. Preoperative biliary drainage is mostly initiated with endoscopic drainage, but endoscopic drainage often fails to obtain adequate drainage (38% failure overall). We present a multi-center study protocol to compare endoscopic and percutaneous drainage in a randomized trial (DRAINAGE-trial), with the broader aim to decrease perioperative morbidity and mortality. Primary outcome measure is the total number of severe preoperative complications between randomization and exploratory laparotomy. In a retrospective comparison of the long-term effects of both drainage methods, we found that overall survival between the endoscopically and percutaneously drained groups was similar (hazard ratio 1.05). These data suggest that both endoscopic and percutaneous drainage can safely be used from an oncological viewpoint.

A new preoperative staging system was developed to predict resectability of perihilar cholangiocarcinoma. Five independent preoperative predictors were found: jaundice, suspected lymph node metastases, Bismuth type, bilateral portal vein involvement, and bilateral hepatic artery involvement. The derived staging system identified 4 classes with resectability rates of 95%, 69%, 50%, and 15%. Since the probability of a resection in class 4 was very low while the risks associated with surgery were very high, these patients might benefit from palliative instead of surgical therapy. The hazards of surgery were further elaborated in a separate risk score predicting postoperative mortality after major liver resection. Postoperative 90-day mortality was 14%, emphasizing the high risks associated with surgery in perihilar cholangiocarcinoma. Patients with a large liver remnant volume after resection (above 50%) seemed to have no benefit from preoperative drainage. Therefore, resection in patients without preoperative drainage in the presence of an FLR volume above 50% may reduce postoperative mortality.

Patients that recover from a resection of perihilar cholangiocarcinoma often develop recurrences. We demonstrated that patients continue to have recurrences beyond four years follow-up until a plateau is reached at about 8 years: the estimated recurrence rate at 8 years after resection was 76%. The high recurrence rate emphasizes the need for adjuvant treatment strategies. In that perspective, accurate risk stratification may identify subgroups that could benefit from adjuvant treatment. A new nomogram for disease-specific survival is proposed: lymph node involvement, resection margin status, and tumor differentiation were independent prognostic factors in the derivation dataset. A nomogram with these factors had good prognostic accuracy in an external validation dataset (concordance index 0.72), which was better than the American Joint Committee on Cancer staging system. The nomogram can inform patients and physicians, guide shared decision-making for adjuvant therapy, and stratify patients in future randomized controlled trials. Incorporating micrometastases in staging systems may further improve their prognostic accuracy. Five-year survival rates in patients with lymph node micrometastases were significantly lower compared to patients without micrometastases (27% versus 54%), and multivariable analysis confirmed micrometastases as an independent poor prognostic factor for survival (hazard ratio 2.4). Finally, we found a different expression profile between intrahepatic and extrahepatic cholangiocarcinoma in 18 of 57 biomarkers that were evaluated in a meta-analysis. These results corroborate earlier findings that intrahepatic and extrahepatic cholangiocarcinoma are distinct forms of cancer. As a consequence, these subgroups should be separated when therapies targeting tumor biology are being considered.