Improving outcomes of minimally invasive pancreas surgery and ampullary cancer

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Chapter 1

General introduction and thesis outline

EPIDEMIOLOGY AND PRESENTATION

Ampullary adenocarcinoma (AAC) is a rare malignancy, accounting for only 0.2%–0.5% of gastro-intestinal cancers[1,2] and about 7% of all periampullary- and pancreatic head cancers.[3] The incidence is around 0.5 case per 100.000 people per year.[4] Compared with other periampullary cancers, AAC generally presents at an early stage of the disease as a result of the biliary obstruction with jaundice it causes.[5] Therefore, at initial presentation, AAC is more amenable to resection as compared to other periampullary cancers (50% versus 20%).[6,7] In addition, patients with AAC have a more favorable prognosis with 5-year survival rates of 30-70% after curative resection.[1,7–11] This wide survival range might be related to the extensive morphological heterogeneity of AAC.

Anatomy and histology

The ampullary region is complex since three anatomically distinct structures adjoin in this region. The confluence of the distal common bile duct and the pancreatic duct represents the ampulla of Vater, this common duct protrudes into the duodenum, which is referred to as the papilla of Vater.[12,13] The ampulla of Vater is named after Abraham Vater, a German anatomist who was the first to describe this anatomical structure in 1720.[14]

As a result of the convergence of these anatomically distinct structures, tumors arising in the ampullary region represent a heterogeneous group with considerable morphological heterogeneity. Different histopathologic subtypes have been described, depending on the epithelium they arise from.[15,16] According to the 4th edition of the WHO classification of tumors, adenocarcinomas of the ampullary region are divided into two main subtypes: intestinal- and pancreaticobiliary subtype.[17] The intestinal subtype arises from the adjacent duodenal mucosa and is characterized by cribriform tubular glands with central necrosis, histologically resembling colonic adenocarcinoma. The pancreaticobiliary subtype derives from the terminal pancreatic or biliary ducts and is characterized by simple or branching glands within a desmoplastic stroma. In addition, a mixed subtype, with overlapping features has been frequently described. Less common subtypes, categorized as 'other' by the WHO, include mucinous carcinoma, poorly cohesive signet ring cell carcinoma, adenosquamous carcinoma, clear cell carcinoma, micropapillary carcinoma, hepatoid adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, and neuroendocrine carcinomas.[17]

Survival

The 5-year overall survival rate after resection of AAC varies from 30% to 70%.[1,7–11] This survival is far more favorable as compared to the 5-year survival rate of patients with pancreatic ductal adenocarcinoma, which is about 20-25%.[18] Of the two main subtypes, the intestinal subtype is associated with a more favorable prognosis compared with the pancreaticobiliary subtype.[15,19–24] Histopathologic characteristics associated with survival,

after adjusting for other risk factors, are lymph node involvement,[22,25–27] pancreaticobiliary subtype,[20–22,28,29] perineural invasion,[21,30,31] lymphovascular invasion[21] and tumor differentiation.[20]

Treatment

The treatment of loco-regional disease consists primarily of surgical resection, a pancreatoduodenectomy (either 'classic Whipple': pylorus-resecting pancreatoduodenectomy, or pylorus-preserving pancreatoduodenectomy).[5] Traditionally, pancreatoduodenectomy, a procedure with high morbidity and mortality rates, is performed through an open approach.[32–34] Recently, minimally-invasive pancreatoduodenectomy (MIPD) has been proposed as an alternative to the open pancreatoduodenectomy (OPD). However, the adoption of minimally invasive techniques (robotic and laparoscopic) in pancreatic surgery have been slow. Presumably, due to the complexity of the procedures, the corresponding high morbidity, and the lack of training possibilities and practical guidance for the implementation of minimally invasive pancreatic surgery. Recently, the first two monocenter randomized controlled trials showed beneficial outcomes in MIPD in terms of a reduced intraoperative blood loss and length of hospital stay, while maintaining oncological resection standards when compared with OPD.[35,36] These favorable findings are supported by several meta-analyses of retrospective studies comparing MIPD with OPD.[37–39] However, a pan-European propensity score matched study comparing MIPD and OPD showed an increased rate of postoperative pancreatic fistula (POPF) after MIPD compared with OPD.[40] Furthermore, the first multicenter randomized controlled trial comparing MIPD with OPD was stopped due to safety concerns.[41] Therefore, it is currently unclear whether MIPD is a valid and safe alternative for OPD.

At present, it is uncertain whether patients with resected AAC gain a survival benefit from adjuvant chemotherapy. Randomized controlled trials focusing specifically on AAC are lacking. The most recent high-level evidence regarding adjuvant chemotherapy in AAC derives from the ESPAC-3 trial, which was conducted in patients with pancreatic head- and periampullary cancer. A subgroup analysis including patients with AAC did not show a survival benefit from adjuvant chemotherapy.[42] On the contrary, several retrospective studies have described an association between adjuvant chemotherapy and an improved survival.[27,43–46]

THESIS OUTLINE

The aim of this thesis is to improve curative-intent treatment and prognosis of patients with ampullary adenocarcinoma. To that end, the studies described in this thesis focus on I) minimally invasive pancreas surgery and II) long-term outcomes of ampullary adenocarcinoma.

Part I: Minimally invasive pancreas surgery

In **chapter 2**, the development and validation of the first evidence-based guidelines for minimally invasive pancreas surgery are described. The recommendations provide guidance for clinical practice of minimally invasive pancreas surgery. **Chapter 3** defines prerequisites needed prior to start performing minimally invasive pancreas surgery, with the objective to guide safe implementation. **Chapter 4** describes the implementation and learning curve of laparoscopic distal pancreatectomy during the first 11 years in the UK. In **chapter 5**, clinical short-term outcomes of laparoscopic distal pancreatectomy with- and without splenectomy are compared. **Chapter 6** describes the study protocol of a randomized controlled trial comparing splenectomy with autogenic splenic implantation versus standard splenectomy in patients undergoing laparoscopic distal pancreatectomy for benign or low-grade malignant lesions of the left pancreas. The aim is to investigate the immune capacity of autogenic splenic implantation. In **chapter 7**, a comparison of surgical outcomes is performed in patients who underwent minimally invasive- or open pancreatoduodenectomy for ampullary adenocarcinoma specifically. The primary outcome in this chapter is major morbidity.

Part II: Long-term outcomes of ampullary adenocarcinoma

In **chapter 8**, histopathologic predictors of overall- and disease free survival in patients with resected ampullary adenocarcinoma are identified using multivariable Cox proportional hazards models. In **chapter 9**, the benefit of gemcitabine-based adjuvant chemotherapy in the different histopathologic subtypes of ampullary adenocarcinoma is investigated, by using propensity scores to match patients who received adjuvant chemotherapy to those who did not. **Chapter 10** describes the development and external validation of a prediction model for survival after resection of ampullary adenocarcinoma. In addition, four different risk-groups are created and the impact of adjuvant chemotherapy in these risk-groups is investigated.

Research questions addressed in this thesis

Chapter	
2	Based on the current evidence, what are recommendations for performing minimally invasive pancreas surgery?
3	Which prerequisites are required prior to embarking on minimally invasive pancreas surgery, to optimize patient safety?
4	Did the use of the laparoscopic approach in distal pancreatectomy increase during the first 11 years of its use in the UK? Did clinical outcomes change during the study period?
5	Are surgical outcomes after laparoscopic spleen-preserving distal pancreatectomy comparable to outcomes after laparoscopic distal pancreatectomy with splenectomy?
6	Is the Salmonella specific antibody response after vaccination with the Typhim Vi™ polysaccharide vaccine comparable between patients who underwent autogenic splenic implantation during laparoscopic distal pancreatectomy to those who underwent spleen-preserving distal pancreatectomy?
7	Are surgical outcomes comparable after minimally invasive- and open pancreatoduodenectomy when performed for ampullary adenocarcinoma?
8	Which histopathologic characteristics predict overall- and disease free survival after resection of ampullary adenocarcinoma?
9	Do patients with ampullary adenocarcinoma benefit from adjuvant chemotherapy after curative intent resection?
10	Can we create a prediction model to predict individual survival after resection of ampullary adenocarcinoma? Does the impact of adjuvant treatment differ between different risk-groups?

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