It’s all around the ampulla

Summary

In this thesis we assessed the treatment modalities and outcome of patients diagnosed with (peri)ampullary cancer. Periampullary cancer is a heterogeneous group of four different cancers originating in close proximity to the ampulla of Vater, i.e. cancer of the pancreatic head, distal cholangiocarcinoma, duodenal adenocarcinoma, and ampullary cancer. Together they make up only 5% of all gastrointestinal cancers. The incidence, treatment modalities, and overall survival of periampullary cancers in the Netherlands is unknown. The main aim of this thesis was to gain more insight in the characteristics, treatment modalities and survival of patients diagnosed with periampullary cancer, and – more specifically – patients diagnosed with ampullary cancer. The ultimate goal is to use the obtained results to optimize the management and overall survival of patients diagnosed with (peri)ampullary cancer.

Periampullary cancer

First, in **chapter two** we described the treatment modalities and overall survival of 8758 patients diagnosed with non-metastatic periampullary cancer between 2012 and 2018 in the Netherlands. Among these 8758 patients, 68% had pancreatic ductal adenocarcinoma, 13% distal cholangiocarcinoma, 12% ampullary cancer, and 7% duodenal adenocarcinoma. Of the patients diagnosed with non-metastatic ampullary cancer 70% underwent resection, followed by duodenal adenocarcinoma (59%), distal cholangiocarcinoma (56%), and pancreatic ductal adenocarcinoma (35%). Neoadjuvant and/or adjuvant therapy was administered in 22% of the patients with pancreatic ductal adenocarcinoma, 12% with duodenal adenocarcinoma, 7% with distal cholangiocarcinoma, and 7% with ampullary cancer. Irrespective of the primary tumor origin, the majority of adjuvant therapy comprised of adjuvant chemotherapy, the remaining of chemoradiotherapy. Half of the patients (51%) diagnosed with pancreatic ductal adenocarcinoma did not receive any form of (anti-cancer) treatment, compared with 41% for distal cholangiocarcinoma, 32% for duodenal adenocarcinoma, and 27% for ampullary cancer. The three year overall survival was highest for patients diagnosed with non-metastatic ampullary cancer (37%), followed by duodenal adenocarcinoma (34%), and distal cholangiocarcinoma (21%), and was lowest for patients diagnosed with pancreatic ductal adenocarcinoma (11%). In addition, we studied the association between adjuvant therapy and overall survival per tumor origin. Only in patients with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma, a higher overall survival was observed when resection was combined with adjuvant therapy compared with resection alone (HR=0.62 (95% CI 0.55-0.69), p<0.001 and HR=0.69 (95% CI 0.48-0.98), p=0.034, respectively). This

association was not found in patients diagnosed with ampullary cancer (HR=0.87 (95% CI 0.62-1.22), p=0.42) and duodenal adenocarcinoma (HR=0.85 (95% CI 0.48-1.50), p=0.58). In conclusion, this study showed considerable differences between applied treatments and overall survival of patients with one of four periampullary cancers. At this point, adjuvant chemotherapy is only associated with improved overall survival in patients with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma.

Details on the chemotherapy regimens prescribed to patients diagnosed with periampullary cancer in the Netherlands are reported in **chapter three.** In total, 2686 patients diagnosed with periampullary cancer were treated with chemotherapy between 2015 and 2019. Neoadjuvant strategies were not studied due to its limited use in daily clinical practice. The majority of the tumors were pancreatic ductal adenocarcinoma (n=2283), followed by distal cholangiocarcinoma (n=161), duodenal adenocarcinoma (n=167), and ampullary cancer (n=78). In the adjuvant setting, the most frequently administered regimens were gemcitabine for pancreatic ductal adenocarcinoma (67%) and ampullary cancer (30%), capecitabine for distal cholangiocarcinoma (58%), and FOLFOX/CAPOX for duodenal adenocarcinoma (81%). Frequently administered first-line palliative chemotherapies were FOLFIRINOX for pancreatic ductal adenocarcinoma (69%), gemcitabine plus cisplatin for distal cholangiocarcinoma (87%), and FOLFOX/CAPOX for duodenal adenocarcinoma (83%) and ampullary cancer (42%). This population-based study showed that patients diagnosed with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma are treated according to the respective guidelines. Patients diagnosed with duodenal adenocarcinoma are often treated following the colorectal cancer guidelines, while a large variation in chemotherapy regimens was seen in ampullary cancer.

Ampullary cancer

In **chapter four**, we presented the results of a systematic review on the accuracy of the diagnostic approach to ampullary tumors, and more specifically on the ability to differentiate between benign and malignant tumors. Assessment of the resection specimen is currently the gold standard to differentiate between benign and malignant tumors. So far, there is no reference standard for the diagnostic approach. We included 10 articles in our review, which described one or more diagnostic modalities in patients diagnosed with ampullary adenomas and carcinomas. In total, 10 different diagnostic modalities were studied, showing the variation currently used in daily clinical practice. The endoscopic ultrasound and intraductal ultrasound seemed to have the best sensitivity and specificity, although forceps biopsy and PET/CT-scan showed similar results in the individual

studies. However, the number of studies were limited with each a small study population. Additional studies investigating the accuracy of the (combination of) diagnostic modalities is thus essential to develop a definitive diagnostic strategy.

Subsequently, in **chapter five** we focused on patients diagnosed with ampullary cancer. Between 1989 and 2016, 3840 patients were diagnosed in the Netherlands. The age-standardized incidence rate increased from 0.59 per 100,000 in 1989-1995 to 0.68 per 100,000 in 2010-2016. In patients with non-metastatic disease, the proportion of patients who underwent resection without neo- and/or adjuvant therapy increased from 50% in 1989-1995 to 64% in 2010-2016 ($p<0.001$) and resection with neo- and/or adjuvant therapy increased from 3% in 1989-1995 to 8% in 2010-2016 ($p<0.001$). Within the group of patients receiving neo- and/or adjuvant therapy, most patients (76%) received adjuvant chemotherapy. Furthermore, the proportion of patients receiving no (anti-cancer) treatment decreased over time (from 46% in 1989-1995 to 28% in 2010-2016, $p<0.001$). In patients with metastatic disease, a fivefold increase in use of chemotherapy was seen: 4% in 1989-1995 to 28% in 2010-2016 ($p<0.001$). The five year overall survival of patients diagnosed with non-metastatic disease increased from 20% in 1989-1995 to 29% in 2010-2016 (logrank $p<0.001$). In patients with metastatic disease, no statistically or clinically significant improvement in median overall survival was observed between 1989 and 2016 (4.4 months to 5.0 months, logrank $p=0.06$). The time period effect on overall survival among all patients disappeared after the inclusion of treatment modality in the multivariable model. We therefore concluded that the improvement of overall survival seen between 1989 and 2016 could be explained by the change in treatment modalities.

The studies among patients diagnosed with ampullary cancer in the current thesis showed a wide variation in treatment strategies in the Netherlands. This is to be expected since no (inter)national guidelines are available. Hence, we aimed to get more insight in the current management strategies implemented by experts in the field. We therefore performed a survey study among surgeons and medical oncologists worldwide, whom are involved in the management of patients diagnosed with ampullary cancer. The results of the survey study were described in **chapter six.** The survey was sent to members of the Dutch Pancreatic Cancer Group, the International Study Group of Ampullary Cancer, the International Hepato-Pancreato-Biliary Association, the European and International Consortium on Minimally Invasive Pancreatic Surgery and to authors who contributed to (peri)ampullary cancer research. Overall, 217 respondents completed the survey of which 86% worked in a pancreatic expertise center. The performance status of the patient, TNM stage, and resection margin are most frequently taken into consideration when choosing a treatment. Neoadjuvant therapy is considered by

24% of the respondents, while adjuvant therapy is considered by 90%. The majority would opt for adjuvant chemotherapy without radiotherapy, whereby the respondents differentiate between intestinal and pancreatobiliary subtype when prescribing a chemotherapy regimen. For the intestinal subtype, 44% prescribed FOLFOX or CAPOX and 33% (modified) FOLFIRINOX. For the pancreatobiliary subtype, (modified) FOLFIRINOX is considered by half of the respondents, followed by gemcitabine plus capecitabine (39% of the respondents). Our survey study highlights the worldwide variation in the management of patients diagnosed with ampullary cancer, especially regarding the use of neoadjuvant and adjuvant therapy. Although surgical procedures improved, more chemotherapy regimens became available, and the knowledge on histological subtype differentiation and tumor biology increased, international registries and randomized controlled trials are needed to aid evidence-based treatment and to study tailored treatment approaches.

Pancreatic ductal adenocarcinoma

In the (inter)national guidelines for pancreatic cancer, both gemcitabine plus capecitabine and gemcitabine alone are recommended for patients not eligible for modified FOLFIRINOX (mFOLFIRINOX) in the adjuvant setting. **Chapter seven** describes a study comparing adjuvant gemcitabine plus capecitabine and adjuvant gemcitabine alone in patients with pancreatic ductal adenocarcinoma. In the period 2015 to 2019, 164 patients were treated with adjuvant gemcitabine plus capecitabine and 614 patients with gemcitabine alone. Median overall survival for patients treated with gemcitabine plus capecitabine was 31.4 months (95% CI 26.8-40.7) compared with 22.1 months (95% CI 20.6-25.0) for patients treated with gemcitabine (HR=0.71 (95% CI 0.56-0.90), p=0.004). After adjusting for relevant prognostic factors, gemcitabine plus capecitabine remained associated with superior overall survival compared with gemcitabine (HR=0.73 (95% CI 0.57-0.92), p=0.009). The positive effect of gemcitabine plus capecitabine on overall survival was found in both patients with a positive resection margin (HR=0.70 (95% CI 0.51-0.97), p=0.34) and patients with a negative resection margin (HR=0.67 (95% CI 0.47-0.96), p=0.029). The proportion of patients completing six cycles of adjuvant therapy was similar in both treatment groups (70% vs. 63%, p=0.11). These real-world data therefore corroborates the trial findings. Adjuvant gemcitabine plus capecitabine should be preferred over gemcitabine monotherapy in patients diagnosed with pancreatic ductal adenocarcinoma who are not eligible for mFOLFIRINOX.