It’s all around the ampulla

Impact paragraph

Cancer in the periampullary region comprises of pancreatic ductal adenocarcinoma, distal cholangiocarcinoma, duodenal adenocarcinoma, and ampullary cancer. Only 5% of all gastrointestinal malignancies are periampullary cancers. Research and the improvement of clinical care mainly focused on pancreatic ductal adenocarcinoma and cholangiocarcinoma, and on periampullary cancer as one group. Currently, high-level evidence on the role of neoadjuvant and adjuvant systemic therapy is available for patients diagnosed with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma, but not for ampullary cancer and duodenal adenocarcinoma. Real-world data regarding treatment modalities and overall survival per periampullary tumor origin are also limited.

The aims of this thesis were to obtain more insight in the incidence of ampullary cancer in the Netherlands, but also in the treatment modalities and outcomes of patients diagnosed per periampullary cancer origin. This chapter describes the relevance of the obtained results and its impact on current and future research and patient care.

Scientific impact

The findings of this thesis show that although periampullary tumors originate in close proximity from each other, treatment strategies as well as survival rates differ per origin. Ampullary cancer and duodenal adenocarcinoma are more often resected, while the proportion of patients treated with (neo)adjuvant chemotherapy are limited compared with patients diagnosed with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma. In addition, not for each tumor adjuvant chemotherapy is equally effective and the chemotherapy regimens administered differed per periampullary tumor origin.

The optimal treatment of periampullary tumors demands a multidisciplinary approach, which is strengthened by the results presented in this thesis. While patients are diagnosed and treated by gastroenterologists, surgeons and medical oncologists, a major role is reserved for the pathologists. The assessment of the resection specimen by the pathologist determines the origin of the tumor and thus whether and which therapy is suitable. However, the differentiation between the four periampullary cancers is difficult. Thereby, until recently, no standardized pathological work-up was available for patients diagnosed with ampullary cancer. Researchers from the International Study Group on Ampullary Cancer are working on the development of a standardized pathology form. It is expected that in this diagnostic form also consensus on the definitions of the

histological subtypes (i.e., intestinal vs. pancreatobiliary, vs. mixed) will be reached. In ampullary cancer, all subtypes can be observed due to its anatomical location, while in duodenal adenocarcinoma mainly the intestinal, and in pancreatic ductal adenocarcinoma and distal cholangiocarcinoma the pancreatobiliary subtype are seen. As the histological subtype has prognostic and predictive relevance, it is of great importance that all tumors are assessed according to the same criteria. Moreover, with the recent studies showing the survival benefit of neoadjuvant therapy in pancreatic ductal adenocarcinoma, the diagnostic strategies should also focus on techniques to differentiate between the four tumor origins with tumor material other than resection specimens (i.e., biopsies) or using molecular profiling.

Albeit the overall survival of patients diagnosed with ampullary cancer is better and even improving over time compared with the other periampullary cancers, the prognosis remains dismal. We were unable to demonstrate an association between adjuvant therapy and overall survival in ampullary cancer due to the small study population. More research focusing on the efficacy of treatment modalities in large, international multi-center randomized controlled trials among ampullary cancer patients are needed. Such high-level of evidence would result in evidence-based, rather than current consensus-based, treatment in patients with ampullary cancer. Currently, the International Study Group on Ampullary Cancer, with whom we shared our findings and vision on future studies, is designing the first international adjuvant chemotherapy trial in ampullary cancer. Literature suggests that the histologic subtype is a prognostic factor, but also affects the response to systemic therapy. Therefore, subgroup analyses and stratification on histologic subtype should be considered in future trials. While awaiting results, an international ampullary cancer register with the patient- and tumor characteristics, information regarding the diagnostic procedures and treatment modalities, and follow-up could be of great value in answering the existing knowledge gaps.

Implementation and target population

First of all, the findings of this thesis are of value to and will be shared with researchers and physicians interested in periampullary cancer. The insight in daily clinical practice obtained by analyzing real-world data provides mirror information to physicians, as we have shown for the introduction and administration of mFOLFIRINOX in pancreatic ductal adenocarcinoma. Physicians can however observe how - consciously and unconsciously – these studies changed their daily clinical practice over time, while for researchers it exposes new research gaps. Researchers and physicians are notified by our findings by, for example, the recent and future publications of our studies in peer reviewed

journals. In addition, the results have been and will be presented at (inter)national conferences and meetings: GROW Science Day 2020 and 2021 (Maastricht University), the European-African Hepato-Pancreato-Biliary Association Congress 2021 (online), The Pancreas Club Meeting 2021 (online), and the National (NVMO) Oncology Days in November 2022 (The Netherlands). In addition, a Dutch article has been published in the 'Nascholingsmagazine Gastro-enterologie' in April 2022, which was accompanied with a podcast. We aimed to reach researchers and physicians active in the field of surgical and medical oncology, but also gastroenterology and pathology.

Second, the results could be useful in the counseling of patients diagnosed with ampullary cancer and their close ones. With the obtained data, physicians can now see what proportion of the patients are treated with which treatment modality and what chemotherapy regimens are administered. Furthermore, the incidence and survival data presented in this thesis will be visually summarized in fact sheets for both patients and physicians (in development), and published online at the websites of Maastricht UMC+ Comprehensive Cancer Center, the Dutch Pancreatic Cancer Group, and the patient organization Living with Hope. This might be of great value for patients and physicians. It is, however, of great importance to be clear that the efficacy of the neoadjuvant and adjuvant treatment is still unclear. The adverse events of the treatment should be weighed against a possible but undefined benefit. In these conversations, tools (i.e., decision aids) developed to help cancer patients define what is important to them, might be helpful. The Deltaplan Pancreatic cancer decision support tool was launched around World Pancreatic Cancer Day on November 12, 2022. We hope to receive additional funding to complement the tool for patients with ampullary cancer.

Third, the ultimate goal is that the outcome of patients diagnosed with periampullary cancer improves, and in the end, that individualized treatment approaches will optimize patient conditions. In order to do so, larger international study populations per periampullary cancer origin and based on molecular profiling are needed. The Dutch Pancreatic Cancer Group is an excellent example of how collaboration between different stakeholders, such as expert centers, physicians, the Netherlands Cancer Registry, Dutch Institute for Clinical Auditing, the Dutch Digestive Foundation ('Maag Lever Darm Stichting), and the pancreatic cancer patient organization Living with Hope, resulted in improved pancreatic cancer care, extensive registries, and high-quality research. Furthermore, international collaboration is essential to include the necessary number of ampullary cancer patients in future clinical trials, as the number of annually diagnosed patients in the Netherlands is limited (191 patients in 2019).

The international survey study we have conducted could be the foundation for further international collaboration. The majority of the respondents acknowledged the need for an international registry, and were willing to be contacted for future studies.

The results of our research presented in this thesis provide tools for daily clinical practice, but also identify perspectives for further research and treatments which is needed for accurate diagnoses and improved outcome. We therefore consider our research presented in this thesis to be of great value in current patient care.