It’s all around the ampulla

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insights in (peri)ampullary cancer

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Evelien Johanna Maria de Jong

Promotor

Prof. dr. V.C.G. Tjan-Heijnen

Copromotores

Dr. J. de Vos-Geelen
Dr. Ir. S.M.E. Geurts

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Dr. G.A. Cirkel, UMC Utrecht

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CHAPTER 1

General introduction and outline of the thesis

General introduction

Periampullary cancer

Of all gastrointestinal tract cancers, only 5% are periampullary cancers.[1,2] This group of neoplasms comprises of four different cancers originating near the ampulla of Vater: cancer of the pancreatic head, distal cholangiocarcinoma, duodenal adenocarcinoma and ampullary cancer (Figure 1.1A). Epidemiological data on the incidence, treatment modalities, and overall survival of periampullary cancers in the Netherlands are missing. Therefore, in this thesis the patients diagnosed with periampullary cancer, especially ampullary cancer, are studied. Furthermore, the adjuvant therapy of patients diagnosed with pancreatic ductal adenocarcinoma, including cancer of the pancreatic head, is examined.

Cancer of the pancreatic head is the most common origin (82%) of periampullary cancer, followed by ampullary cancer (9%), duodenal adenocarcinoma (6%), and distal cholangiocarcinoma (3%).[3] The anatomy of the periampullary region is complex (Figure 1.1A).[2] The common distal bile duct and pancreatic duct adjoin to form the ampulla of Vater, which then protrudes into the duodenum. The close proximity of all structures makes the differentiation between periampullary cancers on imaging challenging (Figure 1.1B).[4]

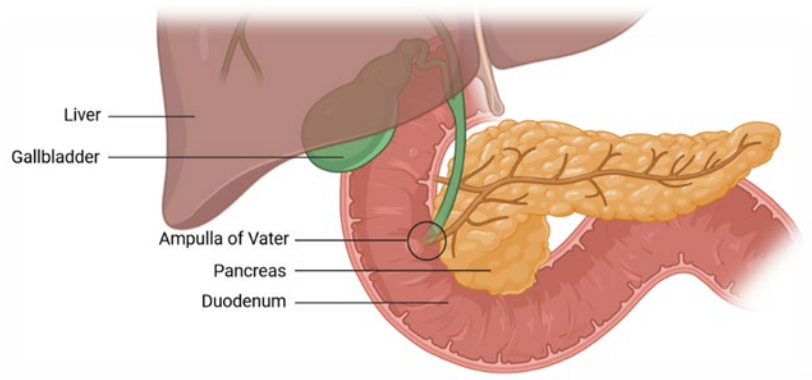

Figure 1.1A – The periampullary region.
Created with BioRender.com (2022).

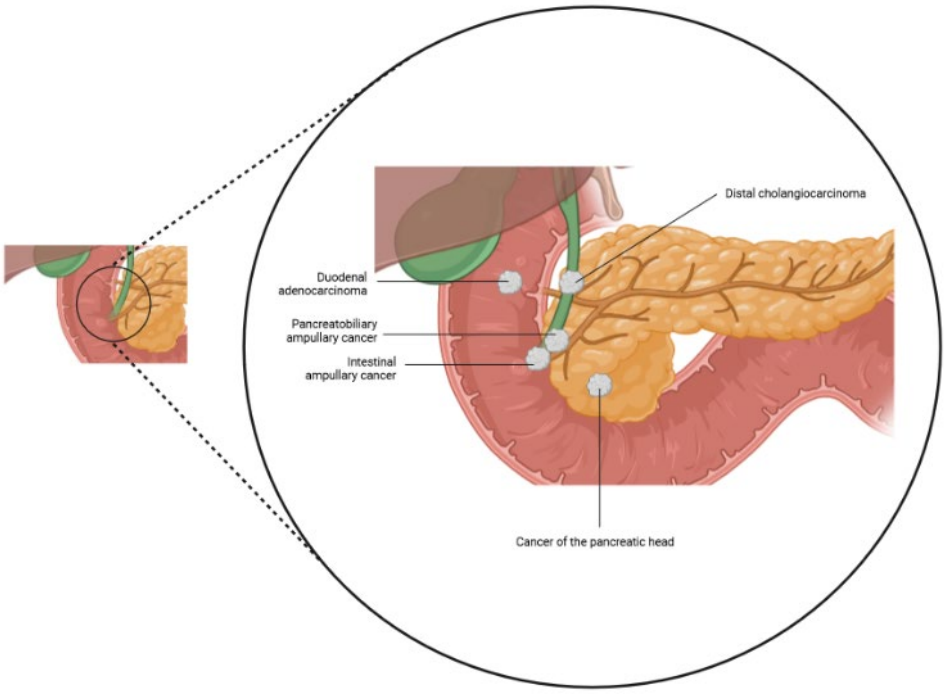

Figure 1.1B – Cancers in the periampullary region.
Created with BioRender.com (2022).

Patients frequently present, irrespective of periampullary tumor origin, with jaundice, abdominal pain, back pain, nausea, vomiting, weight loss, and/or fatigue.[5,6] The diagnostic modalities used to assess the extent of the tumor are (a combination of) abdominal ultrasound, endoscopic ultrasound, and endoscopic retrograde cholangiopancreatography.[5] If possible, biopsy or cytology for histopathological assessment can be obtained simultaneously. Computed tomography and magnetic resonance imaging are used to assess the resectability of the tumor, visualize lymph node involvement, and the presence of distant metastases. All diagnostic information is used to classify tumors according to the Union for International Cancer Control (UICC) Tumor-Node-Metastasis (TNM) classification.[7]

The only curative option for patients diagnosed with periampullary cancer is complete resection of the primary tumor.[5] Pancreatoduodenectomy, with or without preservation of the pylorus, is the surgical procedure of choice.[5,8] However, segmental resection of duodenal adenocarcinoma, and local surgical or endoscopic resection of small ampullary tumors are alternative procedures.[5,9]

Whether the resection should be preceded by neoadjuvant therapy or followed by adjuvant therapy depends on the tumor origin. Currently, only for patients diagnosed with cancer of the pancreatic head and distal cholangiocarcinoma high level evidence and international guidelines are available.[10-15] For patients with pancreatic cancer adjuvant chemotherapy is recommended and more recently neoadjuvant chemotherapy for selected patients as well.[11,12,14] Guidelines for patients with distal cholangiocarcinoma do not recommend neoadjuvant therapy, but are inconsistent on adjuvant therapy.[10,13,15,16] Whereas the National Comprehensive Cancer Network and American Society of Clinical Oncology recommend adjuvant chemotherapy, the European Society of Medical Oncology and Dutch guidelines limit the use of adjuvant chemotherapy to clinical trials. High-level evidence on the benefit of (neo)adjuvant therapy in patients diagnosed with duodenal adenocarcinoma and ampullary cancer is unavailable as randomized controlled trials in these patients are missing.

The majority of the studies on overall survival rates are single-center studies and only include patients who underwent resection.[17-21] Among these patients, median overall survival varied between 54 and 86 months for duodenal adenocarcinoma, 47 and 49 months for ampullary cancer, 22 and 29 months for distal cholangiocarcinoma, and 12 and 19 months for pancreatic cancer. One population-based study (United States of America; 2004-2012), which included both resected and non-resected patients, reported the 5-year overall survival to be highest for ampullary cancer (32%) and duodenal adenocarcinoma (24%), followed by distal cholangiocarcinoma (13%), and pancreatic cancer (7%). The difference in overall survival might be attributed to the location the tumors originate from, resulting in obstructive jaundice at an earlier stage for ampullary cancer compared with the other periampullary cancers.[1-3,22] Furthermore, the histological subtype, i.e. intestinal and pancreatobiliary, is found to be a prognostic factor.[23-25] Patients with an intestinal subtype have a better prognosis compared with patients with a pancreatobiliary subtype.[25] The intestinal subtype resembles tubular adenocarcinoma of the stomach or colon, consisting of well-formed tubular to elongated glands, complex cribriform areas and solid nests.[26,27] This subtype is found in patients diagnosed with duodenal adenocarcinoma and ampullary cancer. The pancreatobiliary subtype is characterized by simple or branching glands and small solid cell-nests enclosed by desmoplastic stroma, and found in patients diagnosed with cancer of the pancreatic head, distal cholangiocarcinoma, as well as ampullary cancer.[26-28]

Ampullary cancer

Ampullary cancer makes up only 0.2% of all gastrointestinal tract cancers, and 7-9% of all periampullary cancers.[29] The age-adjusted incidence rates, reported in

the United States of America, England, and France, vary from 0.46 to 0.63 per 100,000 persons in men and from 0.30 to 0.40 per 100,000 persons in women.[30-32] The incidence of ampullary cancer in the Netherlands is unknown.
High-level evidence on the benefit of neoadjuvant or adjuvant therapy in ampullary cancer is lacking. Only one study regarding adjuvant chemotherapy, the ESPAC-3 trial, performed a subgroup analyses including patients diagnosed with ampullary cancer.[33] No significant survival benefit from adjuvant chemotherapy was seen in ampullary cancer (n=304). The results of prior retrospective studies are inconsistent.[9,34-41] Some studies found an association between adjuvant chemotherapy and improved survival, some reported this benefit only in patients treated with adjuvant chemoradiotherapy, while other retrospective studies and reviews found no association at all.[9,34-38] In 2020, the retrospective study by Moekotte et al. suggested the effectiveness of adjuvant chemotherapy for ampullary cancer might be affected by the histological subtype: the gemcitabine-based adjuvant chemotherapy only resulted in a survival benefit in patients with the pancreatobiliary and mixed subtype and not in patients with the intestinal subtype.[39] Furthermore, studies on the effectiveness of treatment modalities in patients with locally advanced and metastatic ampullary cancer are rarely performed.[40,41] Due to the limited evidence on (neo)adjuvant and palliative therapy, and the lack of international guidelines on the management of ampullary cancer, clinicians might consult guidelines from cancers originating from proximate regions, like the guidelines for pancreatic cancer and biliary tract cancer.[10-12,15,42] As a result, a large variation in the choice of (neo)adjuvant and palliative therapies are expected. However, the details on (neo)adjuvant and palliative therapies administered in daily clinical practice has not been described.

The reported 5-year overall survival for patients diagnosed with ampullary cancer varies from 20% to 50% in recent population-based studies performed in the United States of America, England and France.[3,31,32] Patients who underwent resection have a better overall survival compared with patients who did not: median overall survival of 44 months vs. 9 months.[3] Furthermore, overall survival is affected by TNM stage, resection margin status, perineural invasion, lymphovascular invasion, histological grade, and the histopathological subtype.[43-45]

Pancreatic cancer

Adenocarcinoma of the pancreatic head is the most common of all periampullary cancers. Pancreatic ductal adenocarcinoma has an incidence of 15 per 100,000 persons per year in the Netherlands.[46] These patients are often diagnosed at a more advanced stage (35% stage IV) compared with the other

three periampullary cancers (approximately 24% stage IV).[3,47] Therefore, only 10-20% of all patients diagnosed with pancreatic ductal adenocarcinoma are able to undergo resection of the primary tumor.[46,48] Only patients with (borderline) resectable disease and selected patients with locally advanced disease are suitable for resection. Resectability of the primary tumor is assessed based on the contact of the primary tumor with the superior mesenteric artery, celiac axis, common hepatic artery, and superior mesenteric vein or portal vein.[42] Despite resection of the primary tumor, the majority of the patients develop recurrent disease.[49] To minimize the risk of recurrence, adjuvant chemotherapy is advised.[50] Currently, chemotherapy regimens modified FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) or gemcitabine with or without the oral prodrug of 5-fluorourail capecitabine are recommended.[11,12,42] In addition, several trials studied the efficacy of neoadjuvant chemoradiotherapy. Only in patients with borderline resectable pancreatic adenocarcinoma, neoadjuvant chemoradiotherapy (gemcitabine-based) resulted in more radical resections and improved overall survival.[51,52] Following the preliminary study results, the NCCN already revised their guidelines in 2019 and also the Dutch and other international guidelines are expected to recommend neoadjuvant chemoradiotherapy in patients with borderline resectable cancer. Whether neoadjuvant chemoradiotherapy (gemcitabine-based) is superior to neoadjuvant chemotherapy with FOLFIRINOX, and whether perioperative chemotherapy is superior to adjuvant chemotherapy alone is being studied in the PREOPANC trials (NCT04927780).[53] Patients primarily diagnosed with metastatic disease might be treated with palliative chemotherapy.[11,12,42] Patients will be treated with FOLFIRINOX, or with nab-paclitaxel plus gemcitabine.

Outline of this thesis

This thesis describes the differences in treatment modalities and overall survival between periampullary cancers, and – more specifically – of patients diagnosed with ampullary cancer. All aimed to obtain more insight in this rare entity and to identify areas of improvement to enhance the management and outcomes for patients diagnosed with (peri)ampullary cancer.

In **chapter two** the differences in treatment modalities and overall survival between patients diagnosed with non-metastatic periampullary cancer in 2012-2018 have been assessed. These patients were identified in the Netherlands Cancer Registry (NCR). In **chapter three** the chemotherapy regimens prescribed in patients diagnosed with periampullary cancer in the Netherlands (2015-2019) is described. The regimens of all patients who received systemic therapy were retrieved from the NCR, and the regimens administered as curative and palliative intent were reported per tumor origin. **Chapter four** provides a systematic review of the published literature on the diagnostic approaches of ampullary tumors to assess what (combination of) diagnostic modalities should be used to differentiate between benign and malignant tumors. Subsequently, **chapter five** described the incidence, treatment, and overall survival over time of patients diagnosed with ampullary cancer in the Netherlands. Data of all patients diagnosed between 1989 and 2016 registered in the NCR were used. To obtain more insight in the current management of ampullary cancer, an international survey study was performed among surgeons and medical oncologists. The results of this survey study are presented in **chapter six**. In the final chapter of this thesis, **chapter seven**, the real-world effect of the addition of adjuvant capecitabine to gemcitabine in patients diagnosed with pancreatic ductal adenocarcinoma was evaluated (2015-2019).

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PART I

Periampullary cancer

CHAPTER 2

Treatment and overall survival of four types of non-metastatic periampullary cancer: nationwide population-based cohort study

Evelien J.M. de Jong, Lydia G. van der Geest, Marc G. Besselink, Stefan A.W. Bouwense, Jeroen Buijsen, C.H.C. Dejong, Bas Groot Koerkamp, Lara R. Heij, Ignace H.J.T. de Hingh, Chantal Hoge, Geert Kazemier, Hanneke W.M. van Laarhoven, Vincent E. de Meijer, Martijn W.J. Stommel, Vivianne C.G. Tjan-Heijnen, Liselot B.J. Valkenburg-van Iersel, Johanna W. Wilmink, Sandra M.E. Geurts, Judith de Vos-Geelen for the Dutch Pancreatic Cancer Group

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Abstract

Background
Periampullary adenocarcinoma consists of pancreatic adenocarcinoma (PDAC), distal cholangiocarcinoma (DC), ampullary cancer (AC), and duodenal adenocarcinoma (DA). The aim of this study was to assess treatment modalities and overall survival by tumor origin.

Methods
Patients diagnosed with non-metastatic periampullary cancer in 2012-2018 were identified from the Netherlands Cancer Registry. OS was studied with Kaplan-Meier analysis and multivariable Cox regression analyses, stratified by origin.

Results
Among the 8758 patients included, 68% had PDAC, 13% DC, 12% AC, and 7% DA. Resection was performed in 35% of PDAC, 56% of DC, 70% of AC, and 59% of DA. Neoadjuvant and/or adjuvant therapy was administered in 22% of PDAC, 7% of DC, 7% of AC, and 12% of DA. Three-year OS was highest for AC (37%) and DA (34%), followed by DC (21%) and PDAC (11%). Adjuvant therapy was associated with improved OS among PDAC (HR=0.62; 95% CI 0.55-0.69) and DC (HR=0.69; 95% CI 0.48-0.98), but not AC (HR=0.87; 95% CI 0.62-1.22) and DA (HR=0.85; 95% CI 0.48-1.50).

Conclusion
This retrospective study identified considerable differences in treatment modalities and OS between the four periampullary cancer origins in daily clinical practice. An improved OS after adjuvant chemotherapy could not be demonstrated in patients with AC and DA.

Introduction

Periampullary cancer comprises four different cancer types: pancreatic ductal adenocarcinoma (PDAC), distal cholangiocarcinoma (DC), ampullary adenocarcinoma (AC), and duodenal adenocarcinoma (DA). Together, they form 5% of all gastrointestinal tract malignancies.[1,2] Adenocarcinoma of the pancreatic head is the most common origin of periampullary cancers with 15.56 new diagnoses per 100,000 persons in the Netherlands in 2017, but the other origins are rare (DC 1.29 per 100,000, DA 0.98 per 100,000, and AC 0.96 per 100,000; crude incidence rates).[3] However, pre-operative differentiation on imaging between these four origins is challenging, due to anatomical close proximity. Often, pathological assessment is therefore needed. Importantly, treatment choices and the prognosis are affected by the primary tumor origin.[2]

Pancreatoduodenectomy and segmental resection for DA, are the only potentially curative treatment options for all four tumors.[2,4] International and Dutch guidelines for PDAC recommend resection and adjuvant therapy, whereas international guidelines for DC are inconsistent in terms of adjuvant chemotherapy.[5,6] Neoadjuvant therapy is only recommended in patients diagnosed with borderline PDAC. For AC and DA, no conclusive evidence-based recommendations on neoadjuvant and adjuvant therapy exist and the available evidence on the effectiveness of neoadjuvant and adjuvant therapy is limited.

The reported 5-year overall survival (OS) in population-based studies, irrespective of metastatic disease status, was highest for patients with AC (21-32%), and lowest for patients with PDAC (3-7%).[7,8] No recent nationwide study on resection rates, neoadjuvant and adjuvant therapy and OS in non-metastatic periampullary cancer origins is available.

Therefore, the primary aim of this study was to study the treatment modalities and overall survival in patients diagnosed with non-metastatic periampullary cancer. The secondary aim was to assess the effect of adjuvant therapy on OS for each different anatomic type of periampullary cancer.

Methods

Patient selection

Data of patients initially diagnosed as non-metastatic periampullary adenocarcinoma based on radiological (clinical) staging from January 2012 to

December 2018 (International Classification of Disease-Oncology (ICD-O-3) C17.0, C24.0, C24.1 and C25.0; morphology codes listed in Supplementary Table S2.1) were retrieved from the Netherlands Cancer Registry (NCR).[9] The NCR is a population-based cancer registry in the Netherlands (approx. 17 million inhabitants since 2017), which is linked to the national pathological archive (PALGA), and National Registry of Hospital Discharge Diagnosis to identify all new cancer diagnoses. The notifications are verified in hospital medical records by trained, independent registrars, who also extract information on the patient, tumor, and treatment characteristics.
Patients diagnosed between 2012 and 2018 were included as the centralization of pancreatic surgery in the Netherlands was officially regulated from 2012 onwards.[10-12] Patients younger than 18 years at diagnosis and patients with clinically diagnosed metastatic disease were excluded. Information on vital status was obtained on January 31st 2020 through the Municipal Administrative Database. This study was approved by the scientific committee of the Dutch Pancreatic Cancer Group (DPCG) and the Privacy Review Board of the NCR.[13] According to the Central Committee on Research involving Human Subjects, this study does not require approval from an ethics committee in the Netherlands. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[14]

Definitions

Tumor topography was based on pathologic assessment or, if unavailable, on clinical (imaging) data. Tumor stage was registered according to the (clinical) Union for International Cancer Control (UICC) TNM classification 7th until 2016 and 8th edition from 2017.[15-17] Both clinical TNM (cTNM) and pathological TNM (pTNM-classification) stage were reported. The findings of preoperative oncological work-up (i.e. imaging and consensus most likely diagnosis and staging at multidisciplinary team meeting) including peroperative findings of surgical exploration only were registered as cTNM, and the pTNM stage was based on pathological registered classifications. A final TNM stage consists of pTNM and, if missing, complemented with the clinical registered classifications. In patients treated with neoadjuvant therapy, only clinically registered classifications were used. Patients with unknown tumor classification and/or unknown lymph node involvement were categorized as TNM stage unknown. The pathology report was consulted to obtain information on the assessment of the surgical specimen (i.e. resection margin and histological subtype). Missing information was registered as unknown. Patients who underwent surgical exploration with laparotomy or laparoscopy but no resection of the primary tumor were categorized as no resection. Neoadjuvant and adjuvant therapy regimens were prescribed following the Dutch guidelines (pancreatic cancer, gallbladder cancer, and

colorectal cancer), available evidence, and the recruiting trials. Registration of chemotherapy in the NCR is regardless of the number of chemotherapy cycles patients received.

Endpoints

OS was defined as the time from date of diagnosis to date of death from any cause or censored at last follow-up date. Treatment modalities were categorized as resection only, resection with neoadjuvant and/or adjuvant chemotherapy with or without radiotherapy (in figures shortened to (neo)adjuvant chemo(radio)therapy), chemotherapy alone, radiotherapy alone, chemoradiotherapy without resection, and no (anti-cancer) treatment. A hospital stay after resection exceeding 14 days was considered a proxy for the presence of postoperative complicities (surgical and non-surgical).

Statistical analysis

Dichotomous data are presented as proportions and continuous data as medians with interquartile range. Baseline characteristics between periampullary tumor origins were compared using the chi-square test. The Kruskal-Wallis test was used to compare the median hospital stay between periampullary tumor origins. The percentage of patients undergoing a specific type of multimodality therapy was analyzed for the total group and stratified by tumor origin. The predictive value of patient- and tumor characteristics on receiving adjuvant therapy were studied in patients who underwent resection with logistic regression analyses for each tumor origin. To reduce the risk of immortal time bias, patients deceased within 30 days after resection were excluded. OS was calculated with the Kaplan-Meier method, and the logrank test was used to compare OS between the periampullary tumor origins. Multivariable Cox regression analyses were performed to assess the association between adjuvant therapy and OS in patients who underwent resection and survived at least 30 days, adjusted for age, TNM stage, resection margin, and postoperative hospital stay. A sensitivity analysis was performed among patients who underwent resection, survived at least 30 days, and were diagnosed with TNM stage II or III. In case of multicollinearity, the most relevant parameter to represent a certain variable family was selected based on the -2log likelihood. Variables with a p-value <0.10 in the univariable model were selected for the multivariable model. P-values of <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armong, NY, USA) and STATA SE for Windows, version 14 (StataCorp LP, College Station, Texas, USA).

Results

In total, 8758 patients with clinically non-metastatic periampullary adenocarcinoma were included (Table 2.1). Of these patients, 68% had PDAC, 13% DC, 12% AC, and 7% DA. The median age was 72 years (IQR 64-79 years) in PDAC, 73 years (IQR 65-81 years) in DC, 71 years (IQR 62-80 years) in AC, and 71 years (IQR 62-80 years) in DA. Patients with AC were most often diagnosed at clinical stage I (65%), followed by DC (40%), PDAC (36%) and DA (11%). Of all patients, 7% were found to have metastatic disease (pathological stage IV). Of the patients who underwent resection of the primary tumor, 23% of the patients diagnosed with cTNM stage I were also diagnosed as stage I according to the pathological findings.

Treatment modalities in non-metastatic periampullary adenocarcinoma

Resection of the primary tumor was performed in 70% of the patients with AC, followed by 56% with DC, 59% with DA, and 35% with PDAC (Figure 2.1). Characteristics of the patients who underwent resection (and not deceased within 30 days) are shown in Supplementary Table S2.3. The resection margin was known in 66% of these patients, and a positive resection margin was found in 11% of the patients with AC, 16% of the patients with DA, 31% of the patients with DC, and 45% of the patients with PDAC (Supplementary Table S2.3). Pancreatoduodenectomy was performed most often, and only a small proportion of patients diagnosed with AC (1.0%) or DA (1.2%) underwent a local resection (Supplementary Figure S2.1). For patients who underwent pancreatoduodenectomy, the median length of hospital stay in days (interquartile range) was significantly shorter in patients with PDAC (11 days (9-17)), compared with patients with DC (13 days (9-21)), AC (13 days (9-20)), and DA (13 days (9-22.5); $p<0.001$; Supplementary Table S2.2)). A surgical exploration, without resection, was performed in 11% of the patients with PDAC, 12% with DA, 7% with DC, and 5% with AC.

Table 2.1 – Patient, tumor and treatment characteristics of patients diagnosed with non-metastatic periampullary adenocarcinoma in 2012-2018, by origin (%).

	Total (n=8758)	PDAC (n=5982)	DC (n=1173)	AC (n=1015)	DA (n=585)	Pearson Chi-square
Age						**p=0.046**
<65 years	24.8	24.4	23.5	25.1	31.3	
Median age [IQR], years	72 [65-80]	72 [64-79]	73 [65-81]	71 [62-80]	71 [62-80]	
Sex						**p<0.001**
Male	51.0	48.8	57.1	56.0	52.9	
Clinical tumor classification						**p<0.001**
T1	15.3	11.0	37.3	53.8	5.7	
T2	31.3	34.6	11.5	21.4	12.2	
T3	27.0	26.4	40.3	19.7	29.7	
T4	26.4	28.0	11.0	5.2	52.5	
Unknown	*n=2407*	*n=720*	*n=773*	*n=589*	*n=325*	
Clinical lymph node involvement						**p<0.001**
No	76.6	74.7	81.6	85.9	69.2	
Yes*	23.4	25.3	18.4	14.1	30.8	
Unknown	*n=1153*	*n=756*	*n=165*	*n=137*	*n=95*	
cTNM stage						**p<0.001**
Stage I	37.0	36.2	39.9	64.6	10.6	
Stage II	33.7	32.9	47.1	29.0	36.3	
Stage III	29.4	30.9	13.0	6.4	53.1	
Unknown	*n=2829*	*n=1142*	*n=797*	*n=622*	*n=268*	
TNM stage‡						**p<0.001**
Stage I	15.9	16.2	10.7	25.9	6.8	
Stage II	37.8	38.8	43.0	30.3	29.6	
Stage III	23.5	26.8	9.1	14.3	34.9	
M0 NOS†	16.0	11.0	32.3	25.0	19.0	
Stage IV	6.8	7.3	4.9	4.4	9.7	
Differentiation grade						**p<0.001**
Well	12.2	12.1	14.7	12.3	9.0	
Moderate	52.4	50.8	51.5	57.9	52.4	
Poorly & undifferentiated	35.4	37.2	33.7	29.8	38.7	
Unknown	*n=5095*	*n=3983*	*n=583*	*n=341*	*n=188*	
Histology subtype						**p<0.001**
Intestinal	6.5	2.0	1.4	27.1	27.2	
Pancreatobiliary	6.3	2.8	6.3	11.1	0.0	
Adenocarcinoma, subtype other than IT and PB	13.2	17.9	4.6	3.0	0.5	
Adenocarcinoma, not further specified	74.0	77.4	70.5	58.8	72.3	

Abbreviations: AC=ampullary cancer; DA=duodenal adenocarcinoma; DC=distal cholangio-carcinoma; IT=intestinal; IQR=interquartile range; NOS=not otherwise specified; PB=pancreatobiliary; PDAC=pancreatic ductal adenocarcinoma.

* Positive lymph node involvement includes patients coded as N+ according to UICC 7th edition and patients coded as N1 or N2 according to UICC 8th edition. ‡ TNM stage consists of pathological TNM-classification supplemented with clinical TNM-classification. † M0 NOS: patients without metastatic disease, but could not be grouped based on T-classification (TX) and/or N-classification (NX).

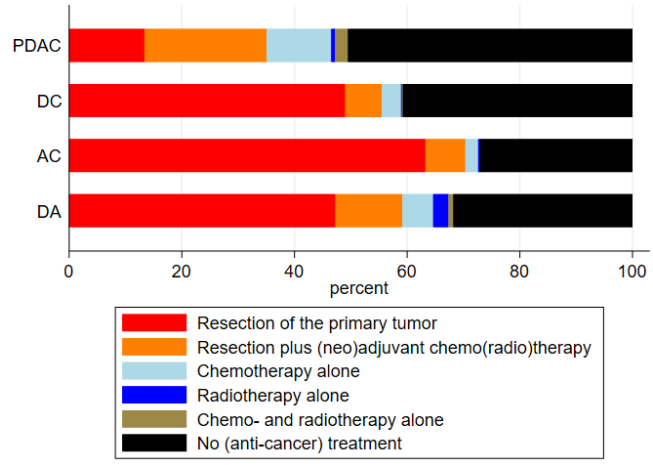

Figure 2.1 – Treatment of 8758 patients diagnosed with non-metastatic periampullary adenocarcinoma in 2012-2018, by origin (%).
Abbreviations: PDAC=pancreatic ductal adenocarcinoma; DC=distal cholangiocarcinoma; AC=ampullary cancer; DA=duodenal adenocarcinoma.

Neoadjuvant and adjuvant therapy were predominantly used in patients with PDAC (58% of resected patients), followed by DA (16%), DC (11%), and AC (11%) (data not further shown). Of the patients who received neoadjuvant and/or adjuvant therapy, the majority (86%) of the patients received adjuvant chemotherapy only, irrespective of primary tumor origin (Figure 2.2).
Chemotherapy alone was administered to 12% of the patients with PDAC, in 5% of the patients with DA, 4% of the patients with DC, and 2% of the patients with AC (Figure 2.1). The highest proportion of patients receiving no (anti-cancer) treatment was seen in PDAC (51%), followed by DC (41%), DA (32%), and AC (27%).

Predictors for adjuvant therapy

Within the group of patients who underwent resection, adjuvant therapy was more often administered in patients <65 years, in patients diagnosed with TNM stage II PDAC and AC, and TNM stage III AC or DC, and in patients diagnosed with PDAC, AC, and DA when hospitalized shorter than 14 days (Table 2.2).

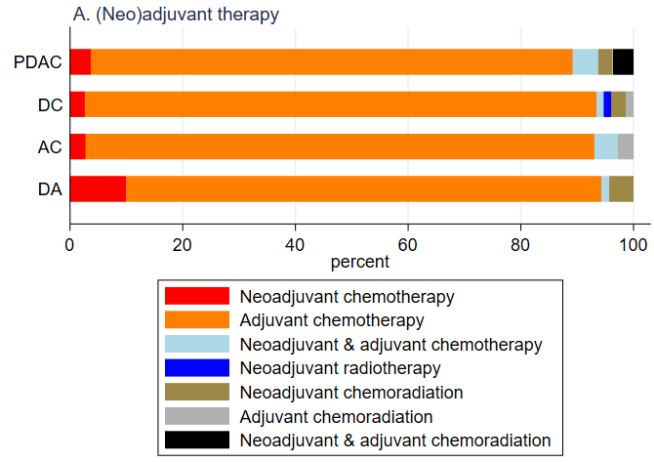

Figure 2.2 – Details of neoadjuvant and adjuvant treatment in 1516 patients diagnosed with non-metastatic periampullary adenocarcinoma in 2012-2018, by origin (%).
Abbreviations: PDAC=pancreatic ductal adenocarcinoma; DC=distal cholangiocarcinoma; AC=ampullary cancer; DA=duodenal adenocarcinoma

Survival

Median OS for all non-metastatic periampullary cancers was 9.8 months (95% CI 9.5-10.1). Three-year and median OS rates were highest for patients diagnosed with AC (37%; 95% CI 34.3-40.1) and 22.6 months), followed by DA (34%; 95% CI 30.4-38.4) and 16.1 months), and DC (21%; 95% CI 18.4-23.4) and 13.1 months), and was lowest for patients diagnosed with PDAC (11%; 95% CI 9.8-11.5) and 8 months); Supplementary Figure S2.2). Patients who underwent resection (Figure 2.3A) had higher three-year OS, compared with patients without resection (Figure 2.3B): 56% vs. 3% in DA, 52% vs. 4% in AC, 35% vs. 3% in DC, and 26% vs. 2% in PDAC.

Median OS was highest for patients with DA, DC and PDAC whom underwent resection with neoadjuvant and/or adjuvant therapy: 71.4 months (95% CI 18.3-24.5) in DA, 28.9 months (95% 22.0-35.7) in DC, and 23.6 months (95% CI 22.1-25.0) in PDAC (Supplementary Figure S2.3). In patients with AC, median OS was highest in those who underwent resection only: 39.9 months (95% CI 32.2-47.6).

Table 2.2 – Multivariable model for characteristics potentially related with receiving adjuvant therapy after resection of the primary tumor, by origin.

Group (no. adjuvant/resected patients)	**Total** (1374/3689=37%)*		**PDAC** (1184/2041=58%)*		**DC** (68/625=11%)*		**AC** (70/691=10%)*		**DA** (52/332=16%)*	
	OR (95% CI); p-value									
Age										
<65 years	Ref.		Ref.		Ref.		Ref.		Ref.	
65-75 years	0.66 (0.56-0.77)	**<0.001**	0.61 (0.49-0.77)	**<0.001**	0.88 (0.51-1.56)	0.688	0.39 (0.22-0.70)	**0.001**	0.53 (0.25-1.10)	0.088
>75 years	0.24 (0.20-0.30)	**<0.001**	0.17 (0.13-0.22)	**<0.001**	0.46 (0.20-1.03)	0.058	0.30 (0.14-0.65)	**0.002**	0.04 (0.01-0.30)	**0.002**
TNM Stage‡										
Stage I	Ref.		Ref.		Ref.		Ref.		Ref.	
Stage II	2.25 (1.78-2.83)	**<0.001**	1.53 (1.11-2.12)	**0.010**	3.41 (0.80-14.49)	0.097	3.70 (1.66-8.26)	**0.001**	1.14 (0.23-5.74)	0.878
Stage III	1.64 (1.25-2.18)	**<0.001**	1.19 (0.79-1.77)	0.408	8.84 (1.89-41.33)	**0.006**	3.41 (1.39-8.38)	**0.007**	4.71 (0.99-22.41)	0.051
M0 NOS	0.58 (0.34-1.00)	0.049	1.46 (0.43-4.94)	0.547	7.10 (1.32-39.32)	**0.023**	1.88 (0.51-6.93)	0.345	0.84 (0.06-11.12)	0.893
Stage IV	0.78 (0.43-1.39)	0.394	0.47 (0.23-0.95)	**0.034**	-	-	4.87 (0.85-28.04)	0.076	-	-
Resection margin status										
R0 resection	Ref.		Ref.		Ref.		Ref.		Ref.	
R1 resection	1.65 (1.34-2.02)	**<0.001**	0.99 (0.76-1.29)	0.912	1.42 (0.73-2.75)	0.306	0.55 (0.15-1.98)	0.356	0.70 (0.20-2.51)	0.588
Unknown	1.00 (0.85-1.18)	0.984	0.89 (0.70-1.12)	0.316	0.78 (0.42-1.44)	0.419	1.30 (0.74-2.29)	0.364	0.63 (0.30-1.33)	0.227
Postoperative hospital stay										
≤14 days	Ref.		Ref.		Ref.		Ref.		Ref.	
>14 days	0.40 (0.34-0.47)	**<0.001**	0.36 (0.29-0.44)	**<0.001**	0.67 (0.38-1.18)	0.164	0.34 (0.17-0.65)	**0.001**	0.37 (0.18-0.78)	**0.008**

Abbreviations: AC=ampullary cancer, CI=confidence interval, DA=duodenal adenocarcinoma, DC=distal cholangiocarcinoma, IQR=interquartile range, NOS=not otherwise specified, PDAC=pancreatic ductal adenocarcinoma

* 123 patients died <30 days after resection (PDAC=58; DC=26; AC=16; DA=23) and were excluded.

‡ TNM stage consists of pathological TNM-classification supplemented with clinical TNM-classification.

Differentiation grade was, despite a p-value<0.05 in the univariable model, not included in the multivariable model based on medical expertise.

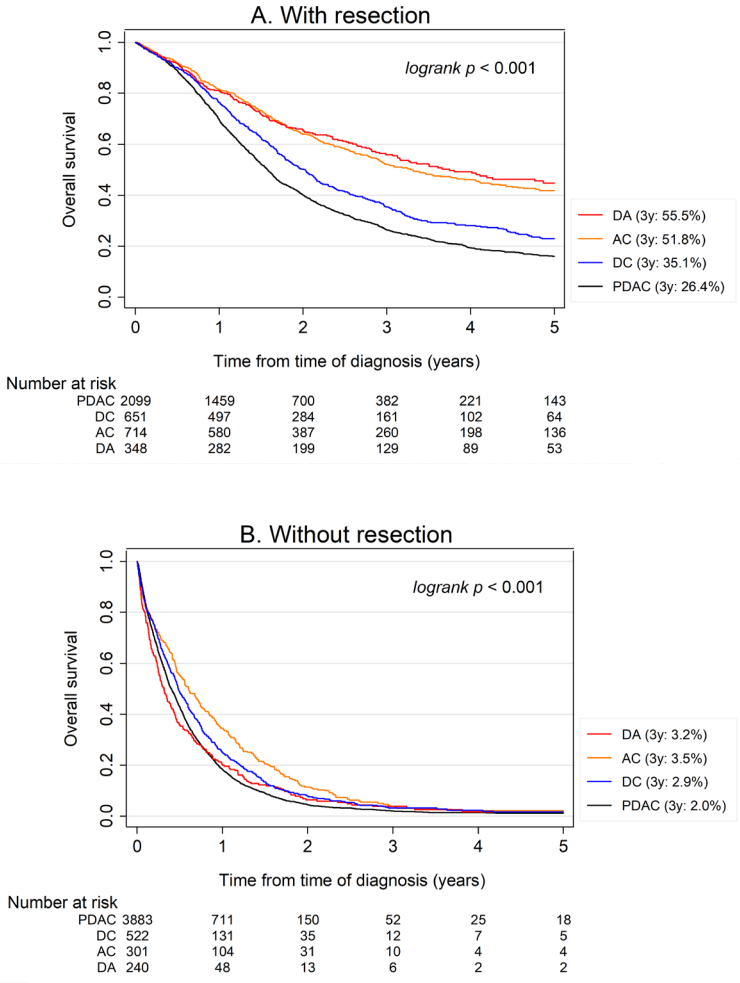

Figure 2.3 – Overall survival in patients with non-metastatic periampullary cancer (A) with resection and (B) without resection.
Abbreviations: PDAC=pancreatic ductal adenocarcinoma; DC=distal cholangiocarcinoma; AC=ampullary cancer; DA=duodenal adenocarcinoma.

After adjusting for age, TNM stage, resection margin, and postoperative hospital stay, resection combined with adjuvant therapy was associated with a higher OS in patients with PDAC (HR=0.62 (95% CI 0.55-0.69), p<0.001), and DC (HR=0.69 (95% CI 0.48-0.98), p=0.038) compared with resection alone, but not in patients with AC (HR=0.87 (95% CI 0.62-1.22), p=0.423), and DA (HR=0.85 (95% CI 0.48-1.50), p=0.580; Table 2.3). The results remained similar when only patients diagnosed with pathological stage II or III were included (data not shown).

Table 2.3 – Multivariable analysis for the association of adjuvant therapy with overall survival in patients who underwent resection of the primary tumor, by origin.

	Total (n=3689)		**PDAC (n=2041)***		**DC (n=625)***		**AC (n=691)***		**DA (n=332)***	
Number of events	2462		1538		423		344		157	
	HR (95%CI); p-value									
Adjuvant therapy										
No	Ref.		Ref.		Ref.		Ref.		Ref.	
Yes	0.90 (0.82-0.98)	**0.013**	0.62 (0.55-0.69)	**<0.001**	0.69 (0.48-0.98)	**0.038**	0.87 (0.62-1.22)	0.423	0.85 (0.48-1.50)	0.580
Age										
<65 years		Ref.		Ref.		Ref.		Ref.		Ref.
65-75 years	1.14 (1.04-1.25)	**0.007**	1.06 (0.94-1.19)	0.321	0.96 (0.77-1.20)	0.747	1.16 (0.90-1.50)	0.264	1.77 (1.16-2.68)	**0.008**
≥75 years	1.28 (1.14-1.43)	**<0.001**	1.13 (0.97-1.31)	0.109	1.23 (0.94-1.61)	0.134	1.07 (0.80-1.44)	0.654	2.30 (1.39-3.83)	**0.001**
TNM-classification‡										
Stage I	Ref.		Ref.		Ref.		Ref.		Ref.	
Stage II	3.02 (2.58-3.54)	**<0.001**	1.79 (1.46-2.18)	**<0.001**	3.50 (2.35-5.21)	**<0.001**	4.67 (3.26-6.70)	**<0.001**	3.36 (1.21-9.35)	**0.020**
Stage III	2.86 (2.39-3.44)	**<0.001**	1.90 (1.50-2.43)	**<0.001**	4.76 (2.86-7.94)	**<0.001**	6.86 (4.65-10.13)	**<0.001**	3.32 (1.18-9.33)	**0.023**
Stage M0 NOS	1.42 (1.01-1.99)	0.041	0.49 (0.15-1.54)	0.219	2.62 (1.41-4.85)	**0.002**	2.52 (1.37-4.64)	**0.003**	3.66 (1.06-12.62)	**0.040**
Stage IV	8.05 (6.09-10.65)	**<0.001**	4.25 (3.00-6.02)	**<0.001**	19.71 (9.44-41.14)	**<0.001**	16.04 (7.80-33.00)	**<0.001**	8.15 (1.98-33.49)	**0.004**
Resection margin status										
R0 resection	Ref.		Ref.		Ref.		Ref.		Ref.	
R1 resection	1.74 (1.55-1.96)	**<0.001**	1.47 (1.27-1.70)	**<0.001**	1.60 (1.21-2.14)	**0.001**	1.23 (0.77-1.95)	0.392	2.67 (1.49-4.79)	**0.001**
Unknown	1.29 (1.17-1.42)	**<0.001**	1.26 (1.11-1.42)	**<0.001**	1.15 (0.92-1.45)	0.226	1.16 (0.90-1.48)	0.248	1.65 (1.09-2.49)	**0.017**
Postoperative hospital stay										
≤14 days	Ref.		Ref.		Ref.		Ref.		Ref.	
>14 days	1.20 (1.10-1.30)	**<0.001**	1.22 (1.10-1.36)	**<0.001**	1.25 (1.02-1.52)	**0.033**	1.14 (0.91-1.43)	0.245	1.33 (0.92-1.93)	0.132

Abbreviations: AC=ampullary cancer, CI=confidence interval, DA=duodenal adenocarcinoma, DC=distal cholangiocarcinoma, IQR=interquartile range, NOS=not otherwise specified, PDAC=pancreatic ductal adenocarcinoma

* 123 patients died <30 days after resection (PDAC=58; DC=26; AC=16; DA=23) and were excluded.

‡ TNM stage consists of pathological TNM-classification supplemented with clinical TNM-classification.

Discussion

This first nationwide population-based cohort study on non-metastatic periampullary cancers demonstrated that almost two thirds of the patients diagnosed with DC, AC, and DA underwent resection, versus only one third of the patients with PDAC. One out of five patients diagnosed with PDAC and who underwent resection, received at least one cycle of neoadjuvant and/or adjuvant therapy, compared with only one out of ten patients diagnosed with DC, AC, and DA. Between 2012 and 2018, three-year OS was highest with 37% for patients diagnosed with AC, followed by 34% in DA, 21% in DC, and 11% in PDAC. This retrospective study could not demonstrate an improved OS after adjuvant chemotherapy in patients diagnosed with AC and DA.

The higher resection rates in patients diagnosed with AC, followed by patients with DA, DC, and PDAC were also observed in a population-based study performed in the USA (2004-2012).[7] PDAC grow in closer proximity to the veins compared with DC, AC, and DA, and therefore complicates the resectability. In addition, patients with AC tend to present relatively early due to symptoms. In the current study, 65% of patients with AC was diagnosed at clinical stage I, compared with 11%-40% in patients with other periampullary cancers.[1,18] The low resection rate in patients diagnosed with PDAC might also be partly explained by misclassification of the exact primary tumor origin in patients who did not undergo resection.[19] Without pathological examination of the tumor, these patients can be – based on clinical data – classified as the most common tumor origin in that area, i.e. PDAC, automatically resulting in a lower proportion of these patients without resection. Furthermore, patients might have been not fit enough for, or not willing to undergo surgery and/or other (anti-cancer) treatment.

Differences in three year OS found in patients diagnosed with non-metastatic AC (37%), DA (34%), and DC (29%) compared with the lower three year OS in patients with PDAC (11%) are similar to previous population-based studies.[7,8,20] The variation in OS between tumor origins might be explained by differences in tumor stage at diagnosis and resection rates. In addition, histological subtype, response to systemic therapy, and differences in biological behavior, e.g. lymph node metastases, neural invasion, and resection margin status, have been shown to be prognostic factors for survival.[21-23] The proportion of patients with a positive resection margin in this study is remarkably high for patients diagnosed with AC (84%) and DA (69%). This might be explained by differences in pathological examination.

In addition, the use of neoadjuvant and/or adjuvant therapy varied widely between periampullary cancer origins. Patients diagnosed with PDAC received neoadjuvant and/or adjuvant therapy most frequently. Following national guidelines, patients with resectable PDAC receive adjuvant therapy, and

neoadjuvant strategies were mostly applied in prospective trials, such as the phase 3 PREOPANC-1 trial, investigating neoadjuvant chemoradiotherapy vs. upfront surgery.[24,25] International and Dutch guidelines advise not to administer neoadjuvant and adjuvant therapy outside clinical trials in DC and the lack of guidelines for AC and DA might explain the low numbers of these patients treated with neoadjuvant and/or adjuvant therapy.[5,25]

We demonstrated that adjuvant therapy is associated with improved OS in patients diagnosed with PDAC and DC, but this association could not be shown for DA and AC. The benefit of adjuvant therapy in patients with PDAC has been shown by the CONKO-001 trial, and the chemotherapeutic agents demonstrated to be effective in the ESPAC-4 trial and PRODIGE-24 trial are now recommended in the international guidelines.[26-28] In patients with DC, the BILCAP study including biliary cancers (including gallbladder cancer), showed that adjuvant capecitabine resulted in better overall survival compared to observation (HR=0.81 (95% CI 0.63-1.04), p=0.10), and the ACTICCA-1 trial (recruiting since 2014) currently investigates different adjuvant treatment strategies.[29,30] The type of adjuvant treatment in patients with DC in the present study is unknown, but might be similar to these clinical studies and thus may have contributed to the OS difference between patients with DC with and without adjuvant therapy.

The seemingly lack of benefit of adjuvant therapy in DA and AC in our study should be interpreted with caution because of the observational study design, the small number of patients receiving adjuvant therapy, and the possible risk of confounding by indication. And although the association between adjuvant therapy and OS was adjusted for age, TNM-classification, resection margin, and postoperative hospital stay, not all possible confounders (i.e. performance status, histologic subtype) were available. The association is thus studied in a heterogeneous study population. Some retrospective studies have reported more favorable OS with adjuvant chemotherapy in patients diagnosed with DA and AC (DA: HR=0.77 (95% CI 0.68-0.8) and AC: HR=0.82 (95% CI 0.71-0.95).[31,32] Only one trial among patients with DC, AC, and DA, on adjuvant therapy is available and shows a survival benefit for adjuvant gemcitabine (HR=0.70 (95% CI 0.51-0.97), p=0.03) and for fluorouracil plus folinic acid (HR=0.79 (95% CI 0.58-1.08), p=0.13) compared with observation after adjusting for prognostic variables.[33] Moreover, it could be suggested to cluster periampullary cancer, especially AC, based on histologic subtype (i.e. intestinal vs. pancreatobiliary) instead of anatomic location or origin.[34] In a retrospective study on gemcitabine-based adjuvant chemotherapy among patients diagnosed with AC, an improvement in survival was only seen in patients with the pancreatobiliary subtype and not in those with the intestinal subtype.[35] High level evidence should therefore be obtained for patients with pancreatobiliary tumors and patients with intestinal tumors separately.

The results of this study should be interpreted in light of some limitations. In addition to the risks associated with the retrospective cohort design, treatment allocation was not at random and survival differences may be (partly) the result of selection bias. Second, the retrospective and nationwide study design limits the availability of data on patient and tumor characteristics (e.g. comorbidity, performance status), recurrences, number of chemotherapy cycles, and type of systemic therapies. The presence and size of the association between adjuvant chemotherapy and overall survival per periampullary tumor origin might have been affected by the number of chemotherapy cycles and type of systemic therapies. Third, without resection specimens for pathological assessment, the diagnosis of the exact anatomic site of periampullary tumors is difficult.[1,36] However, this represents daily clinical practice in which the exact anatomic site is not always known and also pathological assessment is not always conclusive.[19] Fourth, no distinction could be made between resectable, borderline resectable, and locally advanced disease, while clinical decisions for treatment – especially in PDAC – are often made based on this classification. Therefore, our study includes a heterogeneous patient population with resectable and locally advanced disease status.

Yet, this is the first study among a European population diagnosed with periampullary cancer studying resection rates, neoadjuvant and adjuvant therapy, and overall survival, and assessing the association between adjuvant therapy and overall survival per periampullary origin. This study gives therefore insight in daily clinical practice and identifies areas for future studies to obtain high level evidence.

In conclusion, this nationwide study showed that among the four periampullary cancers, i.e. pancreatic adenocarcinoma, distal cholangiocarcinoma, ampullary cancer, and duodenal adenocarcinoma, each have different treatment approaches and outcomes in clinically non-metastatic disease. Data from randomized controlled trials on the effectiveness of neoadjuvant and adjuvant strategies are to be awaited in patients with ampullary cancer and duodenal adenocarcinoma, but also distal cholangiocarcinoma.

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Supplementary material

Table S2.1 – Selected morphologies based on International Classification of Diseases for Oncology (ICD-O-3).

ICD-O-3 code	Description
8000	Neoplasm, NOS
8001	Tumour cells
8010	Carcinoma, NOS
8011	Epithelioma
8012	Large cell carcinoma, NOS
8020	Carcinoma, undifferentiated, NOS
8021	Carcinoma, anaplastic, NOS
8022	Pleomorphic carcinoma
8031	Giant cell carcinoma
8032	Spindle cell carcinoma, NOS
8033	Pseudosarcomatous carcinoma
8035	Carcinoma with osteoclast-like giant cells
8046	Non-small cell carcinoma
8070	Squamous cell carcinoma, NOS
8082	Lymphoepithelial carcinoma
8140	Adenocarcinoma, NOS
8141	Scirrhous adenocarcinoma
8143	Superficial spreading adenocarcinoma
8144	Adenocarcinoma, intestinal type
8145	Carcinoma, diffuse type
8154	Mixed pancreatic endocrine and exocrine tumor
8160	Cholangiocarcinoma
8163	Pancreatobiliary neoplasm
8201	Cribriform carcinoma
8210	Adenocarcinoma in situ in adenomatous polyp
8211	Tubular adenocarcinoma
8255	Adenocarcinoma with mixed subtypes
8260	Papillary adenocarcinoma, NOS
8261	Adenocarcinoma in villous adenoma
8263	Adenocarcinoma in tubulovillous adenoma
8310	Clear cell adenocarcinoma, NOS
8430	Mucoepidermoid carcinoma
8440	Cystadenocarcinoma, NOS
8480	Mucinous adenocarcinoma
8481	Mucin-producing adenocarcinoma
8490	Signet ring cell carcinoma
8500	Ductal carcinoma, NOS
8510	Medullary carcinoma, NOS
8521	Infiltrating ductular carcinoma
8523	Infiltrating duct mixed with other types of carcinoma
8560	Adenosquamous carcinoma
8570	Adenocarcinoma with squamous metaplasia
8572	Adenocarcinoma with spindle cell metaplasia
8574	Adenocarcinoma with neuroendocrine differentiation
8575	Metaplastic carcinoma, NOS
8576	Hepatoid adenocarcinoma
9990	No microscopic confirmation

Abbreviations: NOS=not otherwise specified.

Table S2.2 - Postoperative outcomes and hospital stay (days) after pancreatoduodenectomy of the primary tumor, by origin.

	Total (n=3640)	PDAC (n=2038)	DC (n=632)	AC (n=693)	DA (n=277)	Chi-square (p-value)
Median hospital stay (IQR)	12 (8-18)	11 (9-17)	13 (9-21)	13 (9-20)	13 (9-22.5)	**<0.001**
>14 day hospital stay (yes, n(%))	1319 (36.2)	659 (32.3)	250 (39.6)	276 (39.8)	134 (48.4)	**<0.001**
>21 day hospital stay (yes, n(%))	667 (18.3)	311 (15.3)	147 (23.3)	136 (19.6)	73 (26.4)	**<0.001**
30-day mortality	116 (3.2)	56 (2.7)	25 (4.0)	23 (3.3)	12 (4.3)	0.05

Abbreviations: AC=ampullary cancer; DA=duodenal adenocarcinoma; DC=distal cholangiocarcinoma; PDAC=pancreatic ductal adenocarcinoma.

Table S2.3 – Patient, tumor and treatment characteristics of patients who underwent resection (not deceased within 30 days), by origin (%).

	Total (n=3689) n (%)	PDAC (n=2041) n (%)	DC (n=625) n (%)	AC (n=691) n (%)	DA (n=332) n (%)
Age					
<65 years	1337 (36)	756 (37)	211 (34)	227 (33)	143 (43)
Median age [IQR], years	68 [61-74]	68 [61-74]	68 [61-74]	69 [62-75]	66.5 [59-74]
Sex					
Male	2038 (55)	1095 (54)	366 (59)	399 (58)	178 (54)
TNM stage‡					
Stage I	513 (14)	214 (11)	76 (12)	194 (28)	29 (9)
Stage II	2318 (63)	1470 (72)	435 (70)	277 (40)	136 (41)
Stage III	623 (17)	287 (14)	69 (11)	131 (19)	136 (41)
M0 NOS†	152 (4)	20 (1)	34 (5)	77 (11)	21 (6)
Stage IV	83 (2)	50 (2)	11 (2)	12 (2)	10 (3)
Resection margin					
Positive	1376 (66)	640 (55)	252 (69)	319 (89)	165 (84)
Negative	707 (34)	520(45)	114 (31)	41 (11)	32 (16)
Unknown	*n=1606*	*n=881*	*n=259*	*n=331*	*n=135*
Postoperative hospital stay					
≤14 days	2247 (64)	1338 (68)	366 (60)	407 (61)	136 (51)
>14 days	1277 (36)	644 (33)	241 (40)	263 (40)	129 (49)
Unknown	*n=165*	*n=59*	*n=18*	*n=21*	*n=67*

Abbreviations: AC=ampullary cancer; DA=duodenal adenocarcinoma; DC=distal cholangiocarcinoma; IQR=interquartile range; NOS=not otherwise specified; PDAC=pancreatic ductal adenocarcinoma.

‡ TNM stage consists of pathological TNM-classification supplemented with clinical TNM-classification.

† M0 NOS: patients without metastatic disease, but could not be grouped based on T-classification (TX) and/or N-classification (NX).

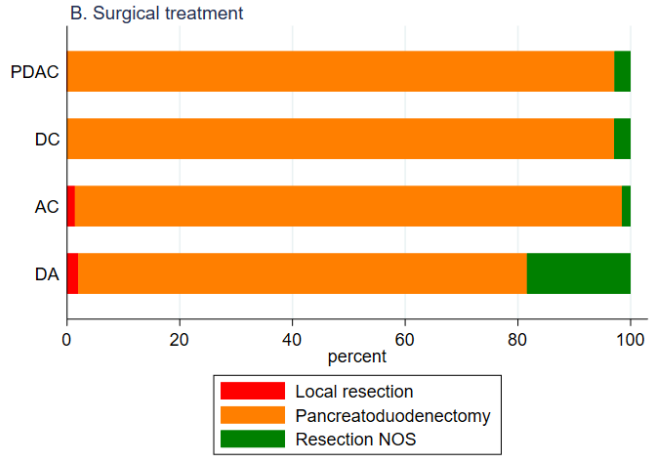


Figure S2.1 – Details of surgical treatment in 3812 patients diagnosed with non-metastatic periampullary adenocarcinoma in 2012-2018, by origin (%).
Abbreviations: PDAC=pancreatic ductal adenocarcinoma; DC=distal cholangiocarcinoma; AC=ampullary cancer; DA=duodenal adenocarcinoma.

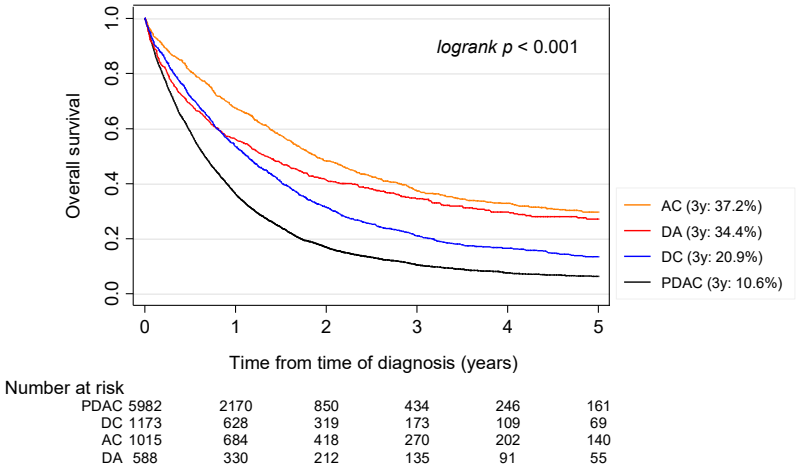
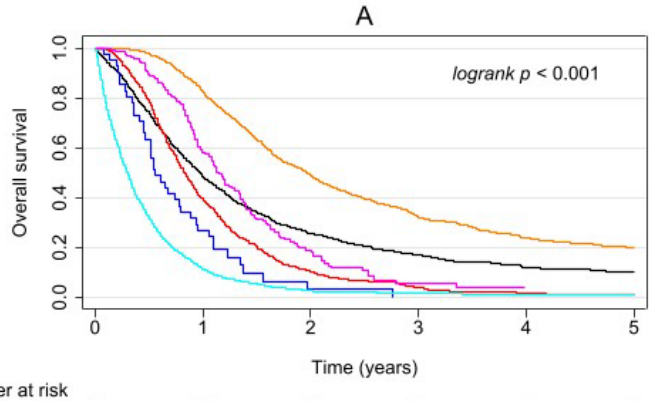
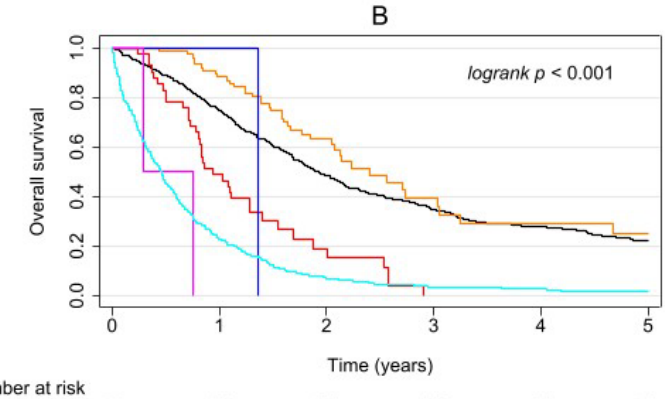


Figure S2.2 – Overall survival of patients with clinically non-metastatic periampullary cancer, by origin.
Abbreviations: PDAC=pancreatic ductal adenocarcinoma; DC=distal cholangiocarcinoma; AC=ampullary cancer; DA=duodenal adenocarcinoma.



Number at risk

Res	800	388	176	98	58	44
Res+	1298	1071	524	284	163	99
CT	685	271	60	16	5	3
RT	41	11	1	0	0	0
CT+RT	137	80	22	4	0	0
No	3021	349	67	32	20	15



Number at risk

Res	575	430	254	149	94	58
Res+	76	67	30	12	8	6
CT	41	20	5	0	0	0
RT	1	1	0	0	0	0
CT+RT	2	0	0	0	0	0
No	478	110	30	12	7	5

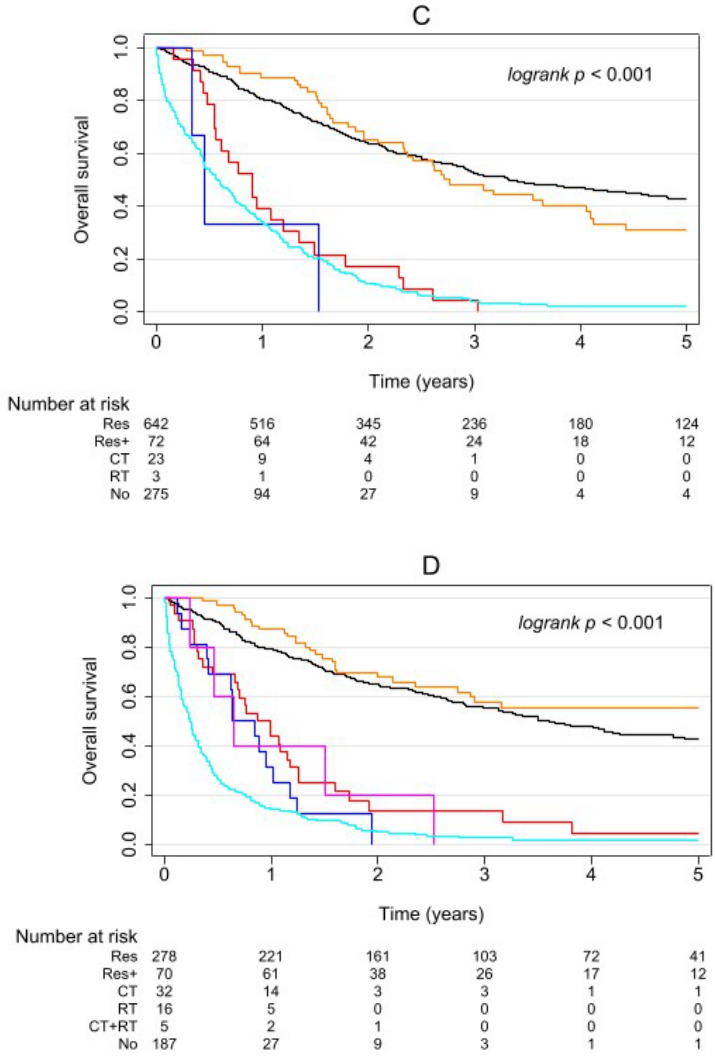


Figure S2.3A-D – Overall survival per treatment modality in patients diagnosed with (A) pancreatic ductal adenocarcinoma, (B) distal cholangiocarcinoma, (C) ampullary cancer, and (D) duodenal adenocarcinoma.

CHAPTER 3

Adjuvant and first-line palliative chemotherapy regimens in patients diagnosed with periampullary cancer: a short report from a nationwide registry

Evelien J.M. de Jong, Irene Mommers, Arantza Fariña Sarasqueta, Lydia G. van der Geest, Lara Heij, Ignace H.J.T. de Hingh, Marjolein Y.V. Homs, Vivianne C.G. Tjan-Heijnen, Liselot B.J. Valkenburg-van Iersel, Johanna W. Wilmink, Sandra M.E. Geurts, Judith de Vos-Geelen for the Dutch Pancreatic Cancer Group

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Abstract

Background
Real-life data on the chemotherapy regimens per periampullary tumor origin has not been reported before. This short report describes the adjuvant and first-line palliative chemotherapy regimens in patients diagnosed with pancreatic ductal adenocarcinoma, distal cholangiocarcinoma, duodenal adenocarcinoma, and ampullary cancer in the Netherlands.

Methods
Patients diagnosed with periampullary cancer in 2015-2019, and treated with adjuvant or palliative chemotherapy, were selected from the Netherlands Cancer Registry. The chemotherapeutic regimens were described per tumor origin, stratified by treatment intent.

Results
In total, 2686 patients were included (1003 treated with adjuvant chemotherapy and 1683 with palliative chemotherapy), of whom 85% had pancreatic ductal adenocarcinoma, 6% distal cholangiocarcinoma, 6% duodenal adenocarcinoma, and 3% ampullary cancer. The dominant adjuvant chemotherapeutic agent(s) administered were gemcitabine and, as of 2019, FOLFIRINOX for pancreatic ductal adenocarcinoma (67% and 17%), capecitabine for distal cholangiocarcinoma (58%), FOLFOX/CAPOX for duodenal adenocarcinoma (81%), and gemcitabine (30%) for ampullary cancer. Most frequently administered palliative chemotherapy combinations were FOLFIRINOX for pancreatic ductal adenocarcinoma, gemcitabine plus cisplatin for distal cholangiocarcinoma, and FOLFOX/CAPOX for duodenal adenocarcinoma and ampullary cancer.

Conclusion
This population-based study gives insight in the real-life chemotherapy regimens used in patients with periampullary cancers. Patients diagnosed with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma were treated according to the respective guidelines and recruiting trials. Duodenal adenocarcinoma was treated following the colorectal cancer guidelines. In ampullary cancer a large variation of chemotherapy regimens was seen.

Introduction

Periampullary cancer comprises of four malignancies arising at close proximity to the ampulla of Vater: ampullary cancer, duodenal adenocarcinoma, distal cholangiocarcinoma and pancreatic ductal adenocarcinoma.[1,2] Together, they make up approximately 5% of all gastrointestinal malignancies. For all entities, resection of the primary tumor is the only curative option.[1,3] However, the role of (neo)adjuvant and palliative chemotherapy differs per tumor origin.[1,3]

The Dutch pancreatic cancer guideline (2019) recommends all (borderline) resectable patients to be treated with adjuvant therapy, in which (modified) FOLFIRINOX is preferred over gemcitabine plus capecitabine.[4,5] In borderline resectable disease, neoadjuvant strategies will be implemented in the updated Dutch guideline (publication in 2022). Patients with locally advanced disease or with metastatic disease and a good performance status are counseled for palliative treatment with FOLFIRINOX. For patients with metastatic disease, older age, or poorer performance status gemcitabine plus nab-paclitaxel is the alternative. For patients diagnosed with distal cholangiocarcinoma, there is no role for neoadjuvant and adjuvant therapy according to the Dutch and European guidelines for biliary tract cancer.[6,7] However, the American Society of Clinical Oncology and National Comprehensive Cancer Network do recommend adjuvant chemotherapy (fluoropyrimidine or gemcitabine-based).[8,9] The recommendation for gemcitabine plus cisplatin in palliative setting is similar in the consulted international guidelines.

For patients diagnosed with ampullary cancer and duodenal adenocarcinoma, no guidelines are available and high-level evidence on the benefit of neoadjuvant and adjuvant chemotherapy is lacking. As a consequence, great variations in chemotherapy regimens are expected as physicians might consult various guidelines for adjacent organs (i.e., pancreas, biliary tract, and colon).

A previous study among periampullary cancer patients reported the proportion of patients treated with chemotherapy in adjuvant or palliative setting in general, without providing detailed information on specific chemotherapeutic agents.[10] Therefore, the aim of this short report is to investigate the adjuvant and palliative chemotherapy regimens administered to periampullary cancer patients diagnosed between 2015 and 2019 in the Netherlands, per tumor origin.

Materials and methods

Patient selection

For this retrospective cohort study, all patients aged 18 years and older, diagnosed with invasive periampullary cancer (Internal Classification of Diseases

for Oncology, third edition (ICD-O-3): C17.0, C24.1, C24.2 and C25.0; Supplementary Table S3.1) between 2015 and 2019 in the Netherlands, and whom were treated with adjuvant or palliative chemotherapy, were selected from the Netherlands Cancer Registry (NCR).[11] In total, 161 patients were excluded as they received neoadjuvant chemotherapy followed by surgery, without receiving adjuvant chemotherapy. In the Netherlands, neoadjuvant therapy has, until recently, only been administered to pancreatic cancer patients who were enrolled in clinical trials. An additional 20 patients were excluded as the type of chemotherapy regimen was not reported. The NCR includes all patients with a newly diagnosed malignancy in the Netherlands, identified by (1) the national pathological archive and (2) the National Registry of Hospital Discharge Diagnosis. Trained administrators collect the data from patients medical records up to approximately nine months after diagnosis.

Definitions

The tumor origin (ICD-O-3 classification) was based on the pathological report available after resection or diagnostic biopsy, and – if not available – on imaging and consensus at multidisciplinary meetings. Tumor stage was classified according to the Union for International Cancer Control (UICC) TNM-classification edition available at the time of diagnosis: the 7th edition for patients diagnosed until 2016 and the 8th edition from 2017.[12,13] Tumor classification and lymph node involvement were based on pathological staging of resection specimens. If missing, or when the patient did not undergo surgery, clinical TNM-classification (preoperative oncological work-up and/or findings at upfront surgical exploration) was used.
Treatment intent was regarded as 'adjuvant' when the patient was diagnosed with TNM stage I-III and underwent resection, and as 'palliative' when the patient was diagnosed with TNM stage IV or did not undergo resection disregarding stage.

Endpoints

In this study, the initial chemotherapy, i.e., adjuvant therapy and the first-line palliative therapy, were described. Initial chemotherapy was defined as all agents administered in parallel within the first thirty days of initiation of chemotherapy. Combinations consisting of fluorouracil (5-FU), oxaliplatin and irinotecan, standard or modified, were classified together as FOLFIRINOX. Time until start of chemotherapy was defined as the time from date of resection to the start date of chemotherapy or, if no resection was conducted, the time from date of diagnosis to the start date of chemotherapy. Overall survival (OS) was

defined as the time from date of diagnosis to date of death from any cause or censored at last follow-up date.

Statistical analyses

Descriptive statistics were used to gain insight in the prescribed initial chemotherapies per tumor origin and treatment intent. OS was calculated with the Kaplan–Meier method.

Results

Patients

Included were 1003 patients receiving adjuvant chemotherapy and 1683 patients receiving palliative chemotherapy (Table 3.1). Median age was 66 years (IQR 58-72) and 55% were male. The majority of the tumors were pancreatic ductal adenocarcinoma (85%), followed by distal cholangiocarcinoma (6%), duodenal adenocarcinoma (6%), and ampullary cancer (3%). The histologic subtype was intestinal in 4% of the patients treated with adjuvant chemotherapy, pancreatobiliary in 11%, other in 45%, and not further specified in 39%. In the palliative group, 5% were intestinal, 1% pancreatobiliary, 6% other, and 86% not further specified. Of the patients treated with adjuvant chemotherapy, 14% received neoadjuvant chemotherapy. The median time until start of chemotherapy was 56 days (IQR 45-70 days) for patients treated with adjuvant chemotherapy and 35 days (IQR 24-56 days) for patients treated with palliative chemotherapy.

Table 3.1 – Patient characteristics.

	Adjuvant chemotherapy (n=1003)	**Palliative chemotherapy (n=1683)**
Age in years, median (IQR)	66 (58 – 72)	66 (58 – 72)
Gender (males), n (%)	554 (55)	923 (55)
Tumor location, n (%)		
Pancreatic ductal adenocarcinoma	853 (85)	1430 (85)
Distal bile duct	65 (7)	96 (6)
Duodenum	52 (5)	115 (7)
Ampulla of Vater	33 (3)	45 (3)
WHO performance status, n (%)		
0	403 (60)	527 (41)
1	227 (34)	605 (47)
2 – 4*	42 (6)	162 (13)

Table 3.1 (continued)

	Adjuvant chemotherapy (n=1003)		Palliative chemotherapy (n=1683)	
Charlson comorbidity index, n (%)				
0	452 (52)		800 (53)	
1	296 (34)		484 (32)	
2	92 (11)		155 (10)	
>2	26 (3)		64 (4)	
TNM stage, n (%)	7th edit.	8th edit.	7th edit.	8th edit.
Stage I	19 (5)	122 (20)	10 (2)	60 (6)
Stage II	326 (86)	247 (40)	52 (9)	81 (8)
Stage III	36 (9)	251 (41)	148 (25)	291 (27)
Stage IV	-	-	378 (64)	649 (60)
T-classification, n (%)	7th edit.	8th edit.	7th edit.	8th edit.
1	16 (4)	72 (12)	20 (4)	49 (5)
2	33 (9)	347 (57)	77 (15)	256 (27)
3	300 (79)	148 (24)	163 (31)	154 (16)
4	29 (8)	43 (7)	266 (51)	503 (52)
N-classification, n (%)	7th edit.	8th edit.	7th edit.	8th edit.
0	91 (24)	173 (28)	31 (53)	46 (45)
1	289 (76)	230 (37)	28 (47)	43 (42)
2	-	217 (35)	-	13 (13)
Histologic subtype, n (%)				
Intestinal	44 (4)		76 (5)	
Pancreatobiliary	108 (11)		21 (1)	
Adenocarcinoma, other subtype	456 (45)		96 (6)	
Not further specified^	395 (39)		1490 (86)	
Neoadjuvant chemotherapy, n (%)‡	140 (14)		4 (0)	
Resection, n (%)	1003 (100)		26 (2)	
Negative resection margin, n (% of patients who underwent resection)	566 (58)		12 (50)	
Time until start of chemotherapy days, median (IQR)				
After resection	56 (45-70)		53 (43-65)	
After diagnosis	-		35 (24-56)	
Overall survival (3-year (%) and median (months)), with 95% CI				
Pancreatic ductal adenocarcinoma	38% (32-41)		9.3 (8.8-9.7) months	
Distal bile duct	40% (NA#)		9.9 (8.5-11.2) months	
Duodenum	61% (NA#)		9.5 (7.8-11.1) months	
Ampulla of Vater	47% (0-60)		11.1 (8.2-14.0) months	

Abbreviations: CI=confidence interval; IQR=interquartile range; WHO=World Health Organization.
* WHO performance status=3 in 30 patients (7 in adjuvant subgroup and 23 in palliative subgroup); WHO performance status=4 in 4 patients (4 in adjuvant subgroup).
^ In this category patients without a pathologically confirmation of the histologic subtype are included.
‡ The number of patients receiving neoadjuvant + adjuvant therapy (type of neoadjuvant chemotherapy regimen administered): pancreatic ductal adenocarcinoma n=138 (FOLFIRINOX=67, gemcitabine=70, nab-paclitaxel plus gemcitabine=1), distal cholangiocarcinoma n=2 (FOLFIRINOX=1, cisplatin plus capecitabine=1), duodenal adenocarcinoma n=1 (CAPOX), ampullary cancer n=3 (FOLFIRINOX).
# The study population was too small to calculate the 95% confidence interval. Missing data, number: WHO performance status 720, Charlson comorbidity index 317, TNM stage 16, T-classification 210, N-classification 1525, Negative resection margin 20.

Chemotherapy regimens

Of the 853 patients treated with adjuvant chemotherapy for pancreatic ductal adenocarcinoma, 570 (67%) patients received gemcitabine alone, 142 (17%) FOLFIRINOX, and 133 (16%) gemcitabine plus capecitabine (Figure 3.1A). In 2018 and 2019, an increase in the proportion of patients treated with FOLFIRINOX was observed (4% in 2015-2017, 20% in 2018, and 53% in 2019) and a decrease in the patients treated with gemcitabine plus capecitabine (83% in 2015-2017, 51% in 2018, and 32% in 2019; Supplementary Figure S3.1). Among the 1430 patients diagnosed with pancreatic ductal adenocarcinoma and treated with palliative chemotherapy, the majority (69%) received FOLFIRINOX (Figure 3.1B). Gemcitabine alone was administered in 225 (16%) patients and gemcitabine plus nab-paclitaxel in 178 (12%).

Among the patients receiving adjuvant chemotherapy for distal cholangiocarcinoma (n=65), most frequent administered chemotherapy regimens were capecitabine (n=38, 58%) and gemcitabine plus cisplatin (n=14, 22%; Figure 3.1A). In the palliative chemotherapy subgroup (n=93), 81 (87%) patients were treated with gemcitabine plus cisplatin, three (3%) with FOLFIRINOX, two (2%) with FOLFOX/CAPOX, and two (2%) with capecitabine (Figure 3.1B).

Of the 52 patients diagnosed with duodenal adenocarcinoma, 42 (81%) patients were treated with adjuvant FOLFOX/CAPOX, nine (17%) received adjuvant capecitabine, and only one patient adjuvant gemcitabine (Figure 3.1A). As palliative chemotherapy, 96 (83%) patients received FOLFOX/CAPOX, and 16 (14%) received capecitabine (Figure 3.1B).

Of patients with ampullary cancer treated with adjuvant chemotherapy, ten (30%) patients received gemcitabine alone, seven (21%) gemcitabine plus capecitabine, six (18%) capecitabine alone, six (18%) FOLFOX/CAPOX, and four (12%) FOLFIRINOX (Figure 3.1A). Of the 45 patients treated with palliative chemotherapy, 19 (42%) were treated with FOLFOX/CAPOX, 11 (24%) with gemcitabine plus cisplatin, five (11%) with FOLFIRINOX, five (11%) with capecitabine, and two (4%) with gemcitabine alone (Figure 3.1B).

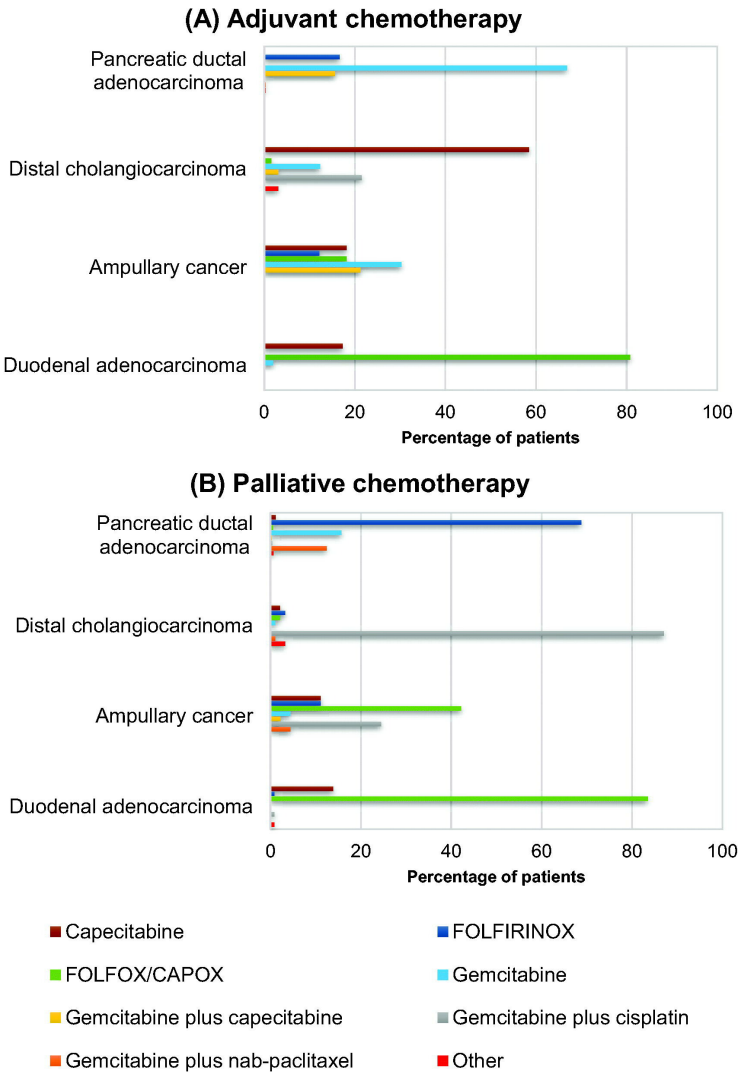

Figure 3.1 – Chemotherapy regimens prescribed in periampullary cancer patients, per tumor origin (in %). Patients treated with (A) adjuvant and (B) palliative chemotherapy*.
Abbreviations: FOLFIRINOX=5-fluorouracil plus irinotecan plus oxaliplatin; FOLFOX/CAPOX=5-flourouracil or capecitabine plus oxaliplatin.
* Distal cholangiocarcinoma, adjuvant: 8=gemcitabine, 2=gemcitabine plus capecitabine, 1=capecitabine plus mitomycin, 1=capectabine plus cisplatin, 1=FOLFOX/CAPOX, Distal cholangiocarcinoma, palliative: 1=docetaxel, 1=gemcitabine, 1=gemcitabine plus carboplatin, 1=gemcitabine plus nab-paclitaxel, 1=gemcitabine plus oxaliplatin. Duodenal adenocarcinoma, palliative: 1=FOLFIRINOX, 1=gemcitabine plus cisplatin, 1=epirubicin plus oxaliplatin plus capecitabine. Ampullary cancer, palliative: 1=gemcitabine plus capecitabine, and 2=gemcitabine plus nab-paclitaxel.

Discussion

This nationwide cohort study is the first to report the contemporary adjuvant and first-line palliative chemotherapy regimens per periampullary tumor origin. For patients treated with adjuvant chemotherapy, the most frequently administered regimens were gemcitabine and, more recently, FOLFIRINOX for pancreatic ductal adenocarcinoma, capecitabine for distal cholangiocarcinoma, FOLFOX/CAPOX for duodenal adenocarcinoma, and gemcitabine for ampullary cancer. Frequently administered palliative chemotherapies were FOLFIRINOX for pancreatic ductal adenocarcinoma, gemcitabine plus cisplatin for distal cholangiocarcinoma, and FOLFOX/CAPOX for duodenal adenocarcinoma and ampullary cancer.

For patients diagnosed with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma, the results are in line with the international and national guidelines.[4-8] Only a limited variation in adjuvant and palliative regimens was seen. Although adjuvant FOLFIRINOX is currently preferred over gemcitabine (plus capecitabine) for pancreatic cancer, gemcitabine alone was more often administered in the first years of the studied timeframe. Firstly, adjuvant gemcitabine was provided in the Netherlands until July 2017 in both arms of the Dutch PREOPANC study investigating the added value of neoadjuvant chemoradiotherapy.[14] Secondly, the results of the PRODIGE-24 trial, which showed a survival benefit of adjuvant mFOLFIRINOX over gemcitabine, were published in 2018 and included in the revised Dutch guideline in 2019.[4,15] For distal cholangiocarcinoma, the applied adjuvant chemotherapy regimens, capecitabine and gemcitabine plus cisplatin, are in line with the inclusion of patients in the ACTICCA-1 trial, which started in 2014 in the Netherlands.[9]

Nationwide population-based studies among patients diagnosed with duodenal adenocarcinoma reported that 16% of the patients in the Netherlands (2012-2018) and 44% of the patients in the United States of America (USA; 2004-2012) received adjuvant chemotherapy.[10,16] The current study showed that patients mainly received FOLFOX/CAPOX as adjuvant and first-line palliative chemotherapy. In the absence of a randomized controlled trial and guidelines, some clinicians apparently treat these patients according to the guidelines for colorectal cancer.[17-19] However, a meta-analysis concluded no difference in the pooled 5-year OS for any type of adjuvant therapy (5-FU based chemo(radio)therapy) compared to observation in patients with duodenal adenocarcinoma.[3] FOLFOX/CAPOX in palliative setting has shown to be associated with an improved survival in a multicenter retrospective study among patients with advanced small bowel cancer, which also included duodenal adenocarcinoma.[20] However, the results may be influenced by treatment selection bias since patients were not randomly assigned to chemotherapy

regimens. No studies assessed chemotherapy regimens in advanced duodenal adenocarcinoma separately.

As result of the lack of high-level evidence and guidelines for ampullary cancer, only a small proportion of patients (10%) diagnosed with non-metastatic disease received adjuvant therapy in the Netherlands (2012-2018), and a large variation in adjuvant and palliative chemotherapy regimens was observed in this study.[10,16] The administered regimens are all recommended in available guidelines for cancers in adjacent organs, which confirms that clinicians prefer to consult guidelines over inconclusive studies. Only the ESPAC-3 trial performed a subgroup analysis on the survival benefit of adjuvant chemotherapy among patients diagnosed with ampullary cancer (n=304), but adjuvant gemcitabine or 5-FU did not improve OS when compared with observation (HR=0.85, 95% CI 0.61-1.18; p=0.323).[21] Observational studies on the efficacy of adjuvant therapy in ampullary adenocarcinoma showed inconsistent results.[22] In future studies on chemotherapy regimens, distinction between the histologic subtypes (intestinal vs. pancreatobiliary vs. mixed type) might be needed as the benefit of gemcitabine-based chemotherapy has shown to be different for each subtype.[23] Yet, the current study shows that tumors are rarely categorized as intestinal, pancreatobiliary or mixed subtype, and therefore decisions are expected not to be affected by histology characteristics.[24,25]

Of note, a quarter of the patients in the current study started adjuvant chemotherapy later than 70 days after resection, which was also observed in previous Dutch studies among pancreatic cancer patients.[26,27] Valle et al. reported that survival was not affected by whether the adjuvant chemotherapy was started <8 weeks or 8-12 weeks postoperatively.[28]

This is the first study to give an overview of the adjuvant and first-line palliative chemotherapy regimens per periampullary tumor origin, reflecting daily clinical practice. However, some limitations of this study should be taken into account. Inherent to the retrospective study design, some data were incomplete or unavailable, e.g., second- and third line chemotherapy regimens. Therefore, treatment adjustments and trajectories could not be studied. In addition, the number of patients included in this study was small and therefore the efficacy of the chemotherapy regimens could not be assessed. Yet, the obtained results can be used to develop new studies on the optimal treatment, especially among larger study populations in ampullary cancer and duodenal adenocarcinoma.

To conclude, this population-based study reflected the limited guidelines available for patients diagnosed with ampullary and duodenal cancer. Patients diagnosed with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma were treated according to the available guidelines and recruiting trials. The chemotherapy regimens in patients diagnosed with duodenal adenocarcinoma were in agreement with the colorectal cancer guidelines, while

the large variation in chemotherapy regimens in ampullary cancer reflects the different guidelines expected to be consulted.

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Supplementary material

Table S3.1 – Selected morphologies based on International Classification of Diseases for Oncology (ICD-O-3)

ICD-O-3 code	Description
8000	Neoplasm, NOS
8001	Tumour cells
8010	Carcinoma, NOS
8012	Large cell carcinoma, NOS
8020	Carcinoma, undifferentiated, NOS
8021	Carcinoma, anaplastic, NOS
8035	Carcinoma with osteoclast-like giant cells
8046	Non-small cell carcinoma
8070	Squamous cell carcinoma, NOS
8140	Adenocarcinoma, NOS
8144	Adenocarcinoma, intestinal type
8160	Cholangiocarcinoma
8163	Pancreatobiliary neoplasm
8261	Adenocarcinoma in villous adenoma
8263	Adenocarcinoma in tubulovillous adenoma
8310	Clear cell adenocarcinoma, NOS
8480	Mucinous adenocarcinoma
8481	Mucin-producing adenocarcinoma
8490	Signet ring cell carcinoma
8500	Ductal carcinoma, NOS
8510	Medullary carcinoma, NOS
8560	Adenosquamous carcinoma
8574	Adenocarcinoma with neuroendocrine differentiation

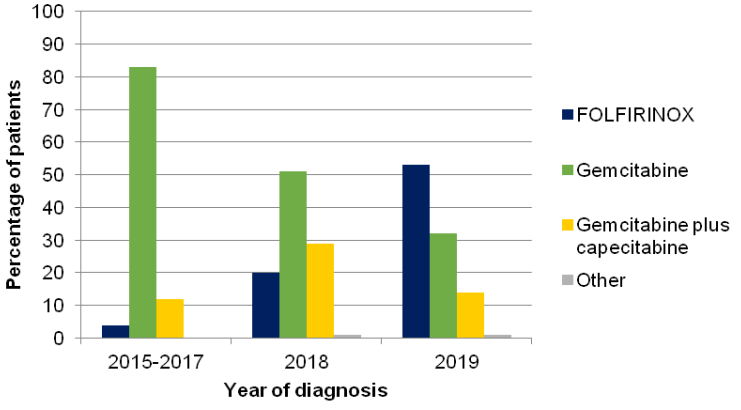

Figure S3.1 – Chemotherapy regimens prescribed in patients diagnosed with pancreatic ductal adenocarcinoma and treated with adjuvant chemotherapy, per period of diagnosis.
Abbreviations: FOLFIRINOX=5-fluorouracil plus irinotecan plus oxaliplatin.

PART II

Ampullary cancer

CHAPTER 4

Diagnostic accuracy of cross-sectional and endoscopic imaging in malignant and benign ampullary tumors – a systematic review

Anouk J. de Wilde*, Evelien J.M. de Jong*, Kurinchi S. Gurusamy, Mohammad Abu Hilal, Marc G. Besselink, Maxime J.L. Dewulf, Sandra M.E. Geurts, Ulf P. Neumann, Steven W.M. Olde Damink, Jan-Werner Poley, Vivianne C.G. Tjan-Heijnen, Judith de Vos-Geelen, Georg Wiltberger, Mariëlle M.E. Coolsen, Stefan A.W. Bouwense
*Shared first authorship

Submitted

Abstract

Background
Differentiation between adenomas and carcinomas of the ampulla of Vater is crucial for therapy and prognosis. This study aimed to review the literature on the accuracy of diagnostic modalities to differentiate between benign and malignant ampullary tumors.

Methods
A systematic literature search was conducted in PubMed, Embase, CINAHL, and Cochrane Library (February 2022). Studies were included if they reported diagnostic test accuracy information among benign and malignant ampullary tumors and used pathological diagnosis as the reference standard. Risk of bias was assessed using QUADAS-2 and QUADAS-C.

Results
Overall, 10 studies encompassing 397 patients were included. Frequently studied modalities were computed tomography (CT; n=2 studies), endoscopic ultrasound (EUS; n=3 studies), intraductal ultrasound (IDUS; n=2 studies), and endoscopic forceps biopsy (n=3 studies). For CT-scan, the reported sensitivity to detect ampullary carcinoma was 44% and 95%, and the specificity 58% and 60%. For EUS, sensitivity ranged between 63% and 89% and specificity between 50% and 100%. A sensitivity of 88% and 100% was reported for IDUS, with a specificity of 75% and 93%. For forceps biopsy, sensitivity ranged between 20% and 91%, and specificity between 75% and 83%.

Conclusion
To differentiate benign from malignant ampullary tumors, EUS and IDUS seem to be the best diagnostic modalities. However, to come to a definitive diagnostic strategy, more high-quality evidence is needed.

Introduction

Adenomas and carcinomas of the ampulla of Vater (hereafter: ampullary tumors) are relatively rare with an incidence of 177 in the Netherlands in 2021 (0.68 per 100,000 in 2010-2016).[1,2] According to autopsy reports, the prevalence of ampullary tumors is only 0.04% to 0.12%.[3] Ampullary tumors can be divided into benign and malignant tumors. Benign tumors have a 26% to 65% life time risk of becoming malignant.[4,5] Patients with benign and malignant tumors largely present with similar symptoms, such as non-specific abdominal complaints, jaundice, and weight loss. In order to differentiate between a benign and malignant tumor and to select the proper treatment, clinicians rely on imaging, visual inspection of the tumor during endoscopy, and histological assessment. However, a clear-cut diagnostic approach to ampullary tumors is lacking.

To assess the local characteristics of the tumor (i.e. size, location, and depth of infiltration) and its relation to surrounding tissues (i.e. involvement of lymph nodes and vascular structures), multiple diagnostic modalities with different advantages and disadvantages are at hand.[6,7] Diagnostic modalities used in daily clinical practice are abdominal ultrasound (US), endoscopy with or without endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreato-graphy (ERCP), magnetic resonance imaging and cholangiopancreatography (MRI/MRCP), computer tomography (CT), positron emission tomography (PET/CT), and nuclear scintigraphy. Of all these diagnostic modalities, EUS and CT-scan are most frequently used. This is in line with the current European Society for Medical Oncology (ESMO) guidelines for the assessment of pancreatic and bile duct tumors.[8,9] Pathological assessment might help to further differentiate between benign and malignant tumors, but sample errors occur frequently.[10,11]

Differentiation between benign and malignant ampullary tumors is especially important to decide which treatment is needed. While for benign ampullary tumors follow-up (with repeating imaging) and local (endoscopic or surgical) resection are available, oncological resection should always be strived for in (suspected) malignant tumors.[6,7,12-15] Not only the risk of malignancy should be taken into account for the proper resection, but also technical success rates and complications of the different procedures should be weighted and discussed with the patient.[16]

A thorough diagnostic assessment is thus important to select the right treatment for the right patient. To date, there is no reference standard for the diagnostic approach to ampullary tumors and no firm scientific data to support a specific diagnostic strategy.[17,18] A previous systematic review on this topic is not available. The aim of this review is to assess the accuracy of the diagnostic approach to ampullary tumors, and more specifically the ability to differentiate between benign and malignant tumors.

Methods

This systematic review was performed according to the Cochrane Handbook and the PRISMA Guidelines, and was registered in PROSPERO database (CRD42021269453).[19-22]

Search strategy

A systematic search was conducted in the PubMed, Embase, Cumulative Index to Nursing & Allied Health Literature (CINAHL), and the Cochrane Library databases to find relevant studies assessing the accuracy of the diagnostic procedures of ampullary tumors. The search was performed on February 4th 2022 and included the following search terms: 'Ampulla of Vater', 'Neoplasms', 'Common Bile Duct Neoplasm', 'Magnetic Resonance Imaging', 'Magnetic resonance cholangiopancreatography', 'Ultrasonography', 'Endoscopic Ultrasound', 'Endoscopy, Digestive System', 'Endoscopic retrograde cholangiopancreatography', 'Tomography, 'X-Ray Computed', 'Duodenoscopy', 'PET/CT', 'Nuclear scintigraphy', 'Cytology', and 'Biopsy' (full search described in Supplementary Material). Synonyms of these terms were also used in the search. There were no restrictions on language or publication date. Duplicate references were removed and all search results were uploaded into Rayyan, a web app for filtering eligible studies for a systematic review.[23] If no abstract and/or full-text was available, the authors of the respective article were contacted by email to obtain them.

Study selection

All articles were screened by two reviewers (AdW, EdJ) independently on the pre-specified inclusion and exclusion criteria based on title and abstract. Studies were included if they met the following inclusion criteria: (1) patients must have a pathologically confirmed ampullary tumor; (2) studies should assess the diagnostic accuracy of a diagnostic modality using histology as the reference standard; (3) if non-ampullary tumors were included in the study, the diagnostic test accuracy information was available in people with ampullary tumors. Exclusion criteria were: (1) study design such as reviews, letters, book chapters, and case reports; (2) studies which only included malignant or only benign tumors. After the abstract screening, the two reviewers (AdW, EdJ) independently read the potentially useful articles in full-text for final selection.

Data extraction and data collection

The two reviewers (AdW, EdJ) independently screened all articles, extracted the data and assessed the risk of bias. Disagreements were resolved by discussion. When no consensus could be reached, an arbitrator (SB) resolved the disagreements. The relevant data were extracted using a data extraction form. Relevant data included: first author, year of publication, study design (prospective or retrospective cohort studies, cross-sectional studies, or randomized controlled trials), total number of patients included, patient characteristics (i.e., age, sex), number of patients diagnosed with an ampullary tumor (malignant vs. benign), index diagnostic test, reference test, and diagnostic test accuracy information (true positive, false positive, false negative, and true negative).

Risk of bias

The Quality Assessment on Diagnostic Accuracy Studies 2 (QUADAS-2) tool and The Quality Assessment of Diagnostic Accuracy Studies-Comparative (QUADAS-C) tool were used to assess the risk of bias.[24,25] The QUADAS-C is an extension of the QUADAS-2 for comparative studies, in which two or more index tests were performed in the same study population. The risk of bias was assessed in four key domains: patient selection, index test(s), reference standard, and flow and timing. Furthermore, the concerns regarding applicability (patient selection, index test(s), and reference standard) were determined. The degree of bias and applicability were expressed as high, low, or unclear as per the guidance documents.

Statistical analysis

The statistical analysis was performed using Review Manager 5.3 (RevMan), software by Cochrane, for generating forest plots.[26] We plotted the individual study estimates of sensitivity and specificity on forest plots for the different index tests to examine the variation between studies. Meta-analysis was attempted using SAS for calculating the summary sensitivity and specificity. Because of the sparse data, simpler hierarchical models were used for meta-analysis.[27] We used visualization of the forest plots and model fit determined by the -2 log likelihood values to decide on the best model to perform meta-analysis. We also visually inspected the forest plots of sensitivity and specificity to examine potential sources of heterogeneity. However, we did not perform any planned subgroup analyses or meta-regression approach to investigate the heterogeneity because of the sparse data.

Results

Selected studies and characteristics

The search yielded 2910 studies of which 305 were duplicates and were excluded (Figure 4.1). The remaining articles were screened for eligibility. Full text was sought for 112 studies. Finally, 10 studies were included for further analyses.[28-37] Preliminary results from three conference abstracts, which were not published as peer-reviewed articles, were included in the overview of the results but not in the analyses because not all diagnostic test accuracy information was presented.[38-40]

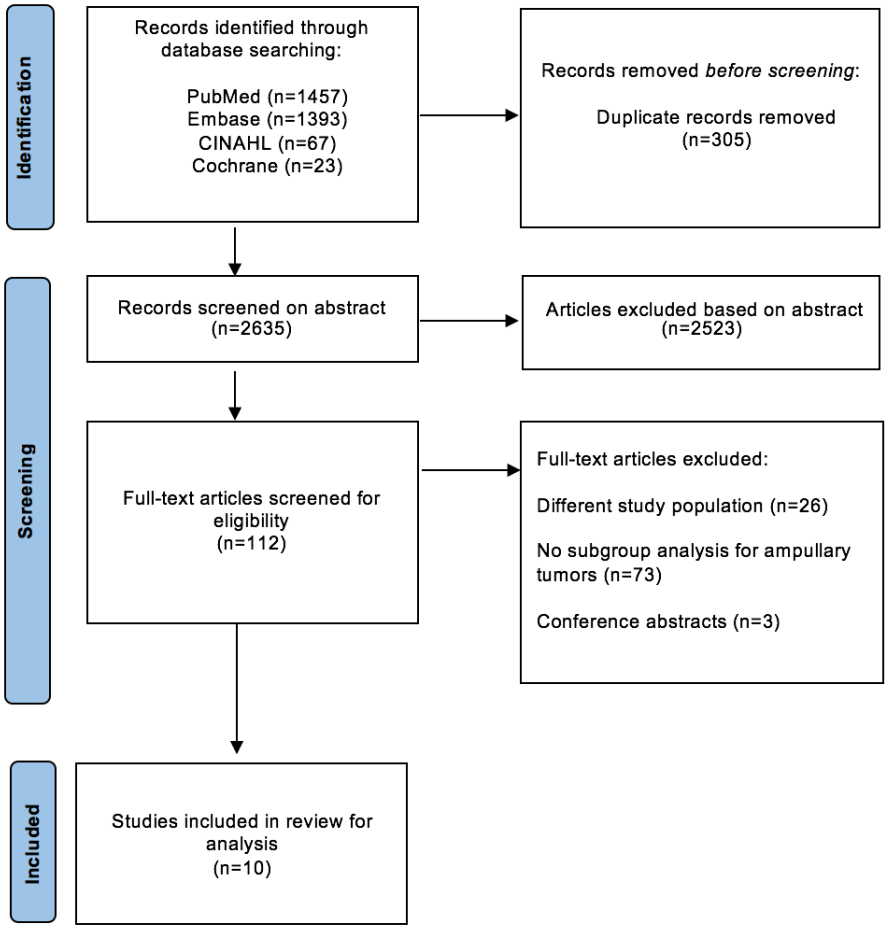

Figure 4.1 – PRISMA flow diagram of search strategy and study selection.

Study characteristics are presented in Table 4.1. Two studies were conducted prospectively and eight retrospectively. The included studies were published between 1997 and 2020 and contained between 24 and 118 patients (total: 397 patients of whom 260 (65,5%) had malignancy. The most frequently studied index tests were EUS[31,32,35] and endoscopic forceps biopsy,[30,32,35] which were both assessed in three studies. Followed by IDUS,[29,32] CT-scan,[33,36] and PET/CT[36,37] which were examined in two studies as index tests. Brush cytology,[28] endoscopic transpapillary biopsy (ETP),[29] biopsy obtained by ERCP,[34] side viewing duodenoscopy (SVD),[35] and a combination of CT-scan with MRI[37] were all studied in one study each. The reference tests in the included studies consisted of pathologic assessment of the resection specimen (obtained by surgical, local and/or endoscopic resection; n=9 studies) or an endoscopic biopsy (n=1 study). In two studies, some patients had long-term follow-up in case of a negative biopsy as reference test.

Quality assessment

The QUADAS-2 tool was used to assess the risk of bias for all included studies. For the studies that compared multiple diagnostic modalities, the QUADAS-C tool was additionally used. In general, the studies have a moderate risk of bias according to the QUADAS-2 (Table 4.2). Manta et al., Rodríguez et al., and Sauvanet et al. rated poorly on patient selection as these studies had inappropriate exclusions and bias was introduced due to the selection procedure.[31,34,35] The reference test in Heinzow et al. was assessed poorly as no histopathological confirmation of the final diagnosis was available for all patients.[29] All studies except of Rodríguez et al.[34] were at high risk of bias in the domain flow and timing. This is mainly due to the fact that different methods of pathology sampling were used as reference tests: resection specimen or biopsy, or follow-up of negative biopsies within one cohort. Regarding applicability concerns, only Bardales et al. and Sauvanet et al. scored poorly on patient selection.[28,35] On all other domains, all studies rated well. Five studies assessed more than one index text, for which the QUADAS-C tool was used.[29,32,35-37] The risk of bias of the QUADAS-C could be interpreted as moderate to poor.

Table 4.1 - Summary of study characteristics of included studies.

Authors	Year	Country	Study design	Sample size	Number of patients with malignant and benign ampullary lesion	Mean age	Index test	Reference standard
Bardales et al.	1997	United States of America	Retrospective cohort study	N=22	Benign; N=15 Malignant; N=7	70 years	Brush cytology	Histology: N=22 biopsy
Heinzow et al.	2011	Germany	Retrospective cohort study	N=72	Benign; N=32 Malignant; N=40	72 years	ETP IDUS	Histology of surgical resection and Long-term-follow-up of negative biopsies *
Ito et al.	2007	Japan	Prospective cohort study	N=40	Benign; N=8 Malignant; N=32	65 years	Endoscopic forceps biopsy	Histology: N=30 surgical resections N=10 endoscopic resections
Manta et al.	2010	Italy	Retrospective cohort study	N=24	Benign; N=5 Malignant; N=19	60 years	EUS	Histology: N=22 surgical resections N=2 endoscopic resections
Menzel et al.	1999	Germany	Prospective cohort study	N=27	Benign; N=12 Malignant; N=15	62 years	IDUS EUS Endoscopic forceps biopsy	Histology: N=27 surgical resections
Pongpornsup et al.	2016	Thailand	Retrospective cohort study	N=55	Benign; N=12 Malignant; N=43	65 years	CT-scan	Histology: Unclear how obtained
Rodríguez et al.	2002	Spain	Retrospective cohort study	N=31	Benign; N=14 Malignant; N=17	Not reported	Biopsy during ERCP	Histology: N=31 surgical resections
Sauvanet et al.	1997	France	Retrospective cohort study	N=26	Benign; N=4 Malignant; N=20	57 years	SVD EUS Endoscopic forceps biopsy	Histology: N=24 surgical resections N=2 endoscopic resections
Sperti et al.	2006	Italy	Retrospective cohort study	N=14	Benign; N=5 Malignant; N=9	65 years	18-FDG PET/CT	Histology: N=14 surgical resections
Wen et al.	2020	China	Retrospective cohort study	N=86	Benign; N=28 Malignant; N=58	62 years	18-FDG PET/CT CT+MRI	Histology: N=48 surgical resections N=10 biopsies N=26 long-term-follow-up

Table 4.1 - continued

ABSTRACTS ONLY								
Authors	**Year**	**Country**	**Study design**	**Sample size**	**Number of patients with malignant and benign ampullary lesion**	**Mean age**	**Index test**	**Reference standard**
Chen et al.	2011	Not reported	Not reported	N=21	Not reported	Not reported	EUS ERCP CT-scan US	Surgical histology
Peng et al.	2018	China	Retrospective cohort study	N=102	Benign; N=76 Malignant; N=18 Nonadenomatous; N=8	60 years	EUS EUS+biopsy	Surgical or endoscopic histology
Sharaiha et al.	2012	United States of America	Retrospective cohort study	N=58	Not reported	63 years	EUS EUS+biopsy	Surgical or endoscopic histology

* The proportion of patients per reference is unclear.

Abbreviations: 18-FDG PET/CT=fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography; CT-scan=computed tomography; ERCP=endoscopic retrograde cholangiopancreatography; ETP=endoscopic transpapillary biopsy; EUS=endoscopic ultrasound; IDUS=intraductal ultrasound; MRI=magnetic resonance cholangiopancreatography; SVD=side viewing duodenoscopy; US=ultrasonography.

Table 4.2 – Quality analysis of included studies: QUADAS-2 and QUADAS-C (patient selection (P), index test (I), reference test (R), flow and timing (FT)).

Study	Test	Risk of bias (QUADAS-2)				Applicability concerns (QUADAS-2)			Risk of bias (QUADAS-C)			
		P	I	R	FT	P	I	R	P	I	R	FT
Bardales et al. (1997)	Brush cytology	✓	✓	?	✗	✗	✓	✓	NA	NA	NA	NA
Heinzow et al. (2011)	ETP	✓	✓	✗	✗	✓	✓	✓	✓	?	✗	✗
	IDUS	✓	✓	✗	✗	✓	✓	✓				
Ito et al. (2007)	Forceps biopsy	✓	✓	✓	✗	✓	✓	✓	NA	NA	NA	NA
Manta et al. (2010)	EUS	✗	✓	✓	✗	✓	✓	✓	NA	NA	NA	NA
Menzel et al. (1999)	EUS	✓	✓	?	✗	✓	✓	✓				
	IDUS	✓	✓	?	✗	✓	✓	✓	✓*	✓*	✗*	✗*
	Forceps biopsy	✓	✓	?	✗	✓	✓	✓				
Pongpornsup et al. (2016)	CT	✓	✓	?	?	✓	✓	✓	NA	NA	NA	NA
Rodríguez et al. (2002)	Biopsy during ERCP	✗	✓	✓	✓	✓	✓	✓	NA	NA	NA	NA
Sauvanet et al. (1997)	EUS	✗	✓	✓	✗	✗	✓	✓				
	SVD	✗	✓	✓	✗	✗	✓	✓	✗*	?*	✓*	✗*
	Forceps biopsy	✗	✓	✓	✗	✗	✓	✓				
Sperti et al. (2006)	CT	✓	✓	?	✗	✓	✓	✓	✓	?	✗	✗
	PET/CT	✓	✓	?	✗	✓	✓	✓				
Wen et al. (2020)	PET/CT	?	✓	✓	✗	✓	✓	✓	✗	✓	✓	✓
	CT+MRI	?	✓	✓	✗	✓	✓	✓				

*Result for all three comparisons

Abbreviations: CT-scan=computed tomography; ERCP=endoscopic retrograde cholangio-pancreatography; ETP=endoscopic transpapillary biopsy; EUS=endoscopic ultrasound; IDUS=intraductal ultrasound; MRI=magnetic resonance cholangiopancreatography; NA=not applicable; PET/CT=positron emission tomography and computed tomography; QUADAS-2=quality assessment on diagnostic accuracy studies 2; QUADAS-C=quality assessment of diagnostic accuracy studies-comparative; SVD=side viewing duodenoscopy; US=ultrasonography.

Diagnostic accuracy

The outcomes reported in the studies are summarized in Table 4.3. The sensitivity and specificity for each index tests were calculated. We attempted a meta-analysis for each index test with more than two studies. However, due to the clinical and methodological heterogeneity along with poor overlap of confidence intervals, convergence was obtained only for fixed-effect meta-analysis, which was clearly inappropriate (because of the poor overlap of confidence intervals). Therefore, meta-analysis was not performed and only a narrative summary is provided below.

Table 4.3 – Summary of the diagnostic test accuracy of the included studies.

Test	Study	Sample size	Outcomes
CT-scan	Sperti et al.	N=14	TP 4; FP 2; FN 5; TN 3 Sensitivity 44% Specificity 60%
CT-scan	Pongpornsup et al.	N=55	TP 41; FP 5; FN 2; TN 7 Sensitivity 95% Specificity 58%
PET/CT	Sperti et al.	N=14	TP 7; FP 4; FN 2; TN 1 Sensitivity 78% Specificity 20%
PET/CT	Wen et al.	N=86	TP 54; FP 6; FN 4; TN 22 Sensitivity 93% Specificity 79%
EUS	Manta et al.	N=24	TP 17; FP 0; FN 2; TN 5 Sensitivity 89% Specificity 100%
EUS	Menzel et al.	N=16	TP 5; FP 4; FN 3; TN 4 Sensitivity 63% Specificity 50%
EUS	Sauvanet et al.	N=26	TP 16; FP 1; FN 4; TN 5 Sensitivity 80% Specificity 83%
IDUS	Heinzow et al.	N=72	TP 28; FP 3; FN 4; TN 37 Sensitivity 88% Specificity 93%
IDUS	Menzel et al.	N=27	TP 15; FP 3; FN 0; TN 9 Sensitivity 100% Specificity 75%
Forceps biopsy	Ito et al.	N=39	TP 29; FP 1; FN 3; TN 6 Sensitivity 91% Specificity 86%
Forceps biopsy	Menzel et al.	N=27	TP 3; FP 3; FN 12; TN 9 Sensitivity 20% Specificity 75%
Forceps biopsy	Sauvanet et al.	N=26	TP 13; FP 1; FN 7; TN 5 Sensitivity 65% Specificity 83%
CT+MRI	Wen et al.	N=86	TP 52; FP 18; FN 6; TN 10 Sensitivity 90% Specificity 36%
SVD	Sauvanet et al.	N=26	TP 10; FP 0; FN 6; TN 10 Sensitivity 63% Specificity 100%
Brush cytology	Bardales et al.	N=12	TP 7; FP 0; FN 0; TN 5 Sensitivity 100% Specificity 100%
ETP	Heinzow et al.	N=62	TP 22; FP 0; FN 0; TN 40 Sensitivity 100% Specificity 100%

Table 4.3a – continued.

Test	Study	Sample size	Outcomes
IDUS+ETP	Heinzow et al.	N=72	TP 31; FP 3; FN 1; TN 37 Sensitivity 97% Specificity 93%
Biopsy during ERCP	Rodríguez et al.	N=31	TP 14; FP 3; FN 7; TN 7 Sensitivity 67% Specificity 70%

Abbreviations: CT-scan=computed tomography; ERCP=endoscopic retrograde cholangio-pancreatography; ETP=endoscopic transpapillary biopsy; EUS=endoscopic ultrasound; FN=false negative; FP=false positive; IDUS=intraductal ultrasound; MRI=magnetic resonance cholangio-pancreatography; PET/CT=positron emission tomography and computed tomography; SVD=side viewing duodenoscopy; TN=true negative; TP=true positive; US=ultrasonography.

CT-scan

In two studies, the results of the sensitivity and specificity of the CT-scan were reported. The sensitivity was 44% in Sperti et al. and 95% in Pongpornsup et al.[33,36] The reported specificity was 58% in Pongpornsup et al. and 60% in Sperti et al. Figure 4.2a shows the forest plot with the corresponding confidence intervals.

PET/CT

Sperti et al. and Wen et al. reported a sensitivity of 78% and 93% for PET/CT with a corresponding specificity of 20% and 79%, respectively.[36,37] The forest plot of the sensitivity and specificity and their corresponding confidence intervals are shown in Figure 4.2b.

EUS

Three studies reported on EUS which used pathological resection specimens as reference test.[31,32,35] The reported sensitivity was between 63% and 89%, and the specificity between 50% and 100%. Figure 4.2c shows the forest plot of the sensitivity and specificity with their corresponding confidence intervals.

IDUS

In two studies the results of IDUS, compared with pathology of resection specimens, were reported. Heinzow et al. reported a sensitivity of 88% and a specificity of 93%. Menzel et al. reported a sensitivity of 100% and a specificity of 75%.[29,32] The forest plot is shown in Figure 4.2d.

Forceps biopsy

Results on forceps biopsy was reported in three studies.[30,32,35] The biopsies were compared with pathology of resection specimens. The sensitivity ranged

between 20% and 91%, and the specificity ranged between 75% and 83%. The sensitivity and specificity with the corresponding confidence intervals are shown in Figure 4.2e.

A

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pongpornsup et al.	41	5	2	7	0.95 [0.84, 0.99]	0.58 [0.28, 0.85]
Sperti et al.	4	2	5	3	0.44 [0.14, 0.79]	0.60 [0.15, 0.95]

B

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sperti et al.	7	4	2	1	0.78 [0.40, 0.97]	0.20 [0.01, 0.72]
Wen et al.	54	6	4	22	0.93 [0.83, 0.98]	0.79 [0.59, 0.92]

C

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Manta et al	17	0	2	5	0.89 [0.67, 0.99]	1.00 [0.48, 1.00]
Menzel et al	5	4	3	4	0.63 [0.24, 0.91]	0.50 [0.16, 0.84]
Sauvanet et al	16	1	4	5	0.80 [0.56, 0.94]	0.83 [0.36, 1.00]

D

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Heinzow et al	28	3	4	37	0.88 [0.71, 0.96]	0.93 [0.80, 0.98]
Menzel et al	15	3	0	9	1.00 [0.78, 1.00]	0.75 [0.43, 0.95]

E

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ito et al	29	1	3	6	0.91 [0.75, 0.98]	0.86 [0.42, 1.00]
Menzel et al	3	3	12	9	0.20 [0.04, 0.48]	0.75 [0.43, 0.95]
Sauvanet et al	13	1	7	5	0.65 [0.41, 0.85]	0.83 [0.36, 1.00]

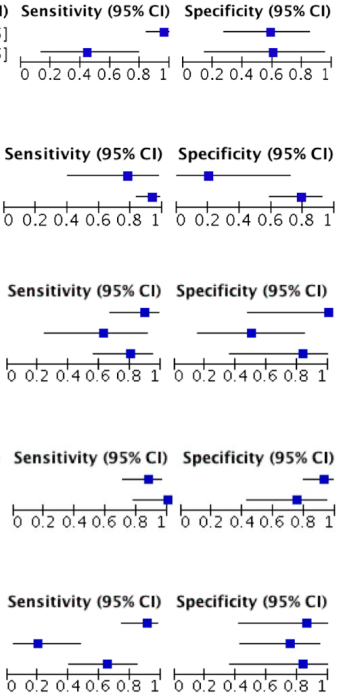

Figure 4.2 – **A.** Diagnostic test accuracy for computed tomography (CT). Random effect model for sensitivity and a fixed effect model for specificity; **B.** Diagnostic test accuracy for positron emission tomography and computed tomography (PET/CT). Fixed effect model for sensitivity and a random effect model for the specificity; **C**. Diagnostic test accuracy for endoscopic ultrasound (EUS). Random effect model for sensitivity and fixed effect model for specificity; **D.** Diagnostic test accuracy for intraductal ultrasound (IDUS). Fixed effect model for sensitivity and a random effect model for specificity; **E.** Diagnostic test accuracy for forceps biopsy. Random effect model for sensitivity and a fixed effect model for specificity.
Abbreviations: TP=true positive; FP=false positive; FN=false negative; TN=true negative; CI=confidence interval.

Additional index tests

Five different index tests were reported only once in five different studies. Bardales et al. reported a sensitivity and specificity of 100% for brush cytology.[28] Endoscopic transpapillary biopsy also had a sensitivity and specificity of 100% according to Heinzow et al.[29] The sensitivity and specificity of biopsy during ERCP

were 67% and 70%, respectively (Rodríguez et al.).[34] For side viewing duodenoscopy, Sauvanet et al. reported a sensitivity of 63% and a specificity of 100%, and Wen et al. reported a sensitivity of 90% and specificity of 36% for CT+MRI.[35,37]

In addition, Table 4.4 shows the diagnostic test accuracy of the conference abstracts which could not be analyzed due to missing diagnostic test accuracy information.[38-40]

Table 4.4 – Summary of the diagnostic test accuracy of the conference abstracts

Abstracts	Test	Outcomes
Chen et al.	EUS, ERCP, CT-scan, US	EUS: Sensitivity 95% ERCP: Sensitivity 95% CT: Sensitivity 19% US: Sensitivity 5% Overall T-staging EUS: Sensitivity 75% CT: Sensitivity 5% US: Sensitivity 0%
Peng et al.	EUS	Sensitivity 80% Specificity 93%
Sharaiha et al.	EUS	Sensitivity 100% Specificity 72% Overall T-staging Sensitivity 66.7% Specificity 91.7%

Abbreviations: CT=computed tomography; ERCP=endoscopic retrograde cholangiopancreatography; EUS=endoscopic ultrasound; US=ultrasonography.

Discussion

This first systematic review on diagnostic modalities in benign and malignant ampullary tumors confirmed the wide variation of diagnostic modalities currently being used in daily clinical practice with EUS and IDUS seemingly having the best sensitivity and specificity. The specificity of forceps biopsy and the sensitivity of the PET-CT were comparable in the individual studies. No meta-analysis could be performed due to the clinical and methodological heterogeneity and poor overlap of confidence intervals between the studies.

Correct diagnosis of ampullary tumors is important, since an oncological resection is indicated in case of a malignant tumor in contrast with benign tumor for which follow-up or a local resection is possible. The diagnostic approach in daily clinical practice to patients with an ampullary tumor is based on the guidelines for patients suspected of pancreatic cancer. The ESMO guideline advises to perform

a CT-scan in all patients, and in case of doubt an EUS.[9] Fine needle aspiration and biopsy to obtain cytology or histology might be considered for further differentiation.[8] On the contrary, the European Society of Gastrointestinal Endoscopy (ESGE) guideline on the endoscopic management of ampullary tumors considers an endoscopic biopsy mandatory in the diagnostic work-up.[15] However, ESGE admits the level of evidence is weak due to the wide range of accuracy reported for preprocedural biopsy.

The reported sensitivity of CT-scan in the two included studies (44% and 95%) are highly variable and do not convincingly support the choice for CT-scan by the ESMO.[33,36] It should be noted that the study populations were small, heterogeneous in terms of pathology sampling methods, and that in the study by Pongpornsup et al. different protocols, i.e. non-contrast, porto-venous, venous, arterial and delayed phases, were used to acquire the images.[33] The sensitivity and specificity reported in the included studies for EUS and IDUS are higher, resulting in less false negative and false positive test results compared to CT-scan. In addition, several studies show that EUS can also be used for tumor classification according to the TNM stage criteria, which can be useful in choosing the proper treatment.[41-43]

The findings in the current study do correspond with the 2017 systematic review by Veereman et al. that assessed which tests are the best to differentiate between benign and cancerous pancreatic tumors.[44] Only 11 studies with a limited number of patients were included by Veereman et al, which resulted in large confidence intervals. They judged that the methodological quality of the included studies was very low, also due to poor patient selection and the different reference tests used within one study. The heterogeneity and poor methodological quality of 54 studies included in the Cochrane systematic review by Best et al. also prevented from concluding the diagnostic accuracies of imaging modalities in patients with focal pancreatic tumors.[45]

In daily clinical practice, the proper treatment is preferably selected based on the pathological confirmation of the diagnosis. Local (endoscopic and surgical) and oncological resections are options, but also follow-up with repetitive imaging might be considered. The value of periodical image follow-up as diagnostic modality has not been studied in the current included studies, while for small ampullary tumors this could be an appropriate alternative to endoscopic or surgical resection, particularly in frail patients when the biopsy does not show any high risk features suggestive of malignancy.[15] No consensus regarding the appropriate follow-up period exists, but the ESGE guideline advises an interval period of three months between diagnostic modalities during follow up.[15] In patients in whom resection is contemplated, determining the resectability of the tumor is the most important aspect to decide what resection procedure should be considered.[46] From that point of view, the choice for CT-scan in the

pancreatic cancer guideline is understandable as also ingrowth in nearby structures and involvement of lymph nodes and metastases can be visualized. However, EUS and IDUS are also likely to indicate the local infiltration, although they are unlikely to provide information about lymph node involvement or distant metastases. Besides, pathological assessment is advised prior to starting chemotherapy in a neoadjuvant or palliative setting.[8] CT scan and endoscopy are the main modalities from which biopsies can be obtained.

When considering what diagnostic modality is preferred, the patient burden and costs should also be taken into account. Imaging modalities such as CT-scan, with or without PET, are less invasive than EUS and IDUS. With the invasive procedures, especially when combined with a biopsy, the risk of complications increases. Perforation of the upper gastrointestinal tract (0.03%), pancreatitis (1% to 2%), bleeding (4%), or complications from the anaesthesia have been reported.[47] Yet, IDUS is hardly used anymore outside the Asian world. The CT-scan is available in most places, which enables patients to visit a hospital close to their home. For EUS, patients might have to travel further as only selected centers do have the right equipment and physicians with the expertise to perform these procedures. In addition, the cost-effectiveness which mainly depends on the accuracy and costs of the test(s) should be taken into consideration.

The majority of studies had a moderate risk of bias, though some studies were considered to be at high risk of bias. Different methods of pathology sampling were used and the reference tests varied within studies, resulting in heterogeneity between the studies. Previous studies have shown that pathological assessment of biopsies is not as accurate as assessment of the surgical specimens.[48,49] On the contrary, if only resection specimens were used as reference standard, this suggests that only patients with high risk of malignancy were included.

There are several limitations of this review. First, due to limited data and heterogeneity, no reliable meta-analysis could be performed. Second, most studies included were retrospective studies. No randomized controlled trials were available on this subject, partly due to the low incidence of ampullary tumors. Despite these limitations, this study is the first to comprehensively review available evidence on diagnostic modalities in patients diagnosed with an ampullary tumor. Furthermore, the risk of bias tools used in this review were specifically developed for diagnostic test accuracy studies (QUADAS-2) and the assessment of test comparisons (QUADAS-C).

The limited number of studies included in this review highlights the need for continued research on this topic. At this moment, no studies are registered at ClinicalTrials.gov or the International Clinical Trials Registry Platform (ICTRP). Large and prospective cohort studies are required by establishment of ampullary tumors registry such as the International Study Group on Ampullary Cancers (ISGACA)[50] will provide information regarding the use and accuracy of diagnostic modalities

in daily clinical practice. In this register, all examinations a patient undergoes in the diagnostic procedure should be registered in such a way that the accuracy of each examination can be studied separately and combined. The biggest challenge for studies is to have an adequate sample size: (inter)national collaboration should be encouraged. Furthermore, there is a need for standardized pathological assessment of both biopsies and resection specimens of malignant and benign tumors in order to assess the diagnostic accuracy of these procedures. This is necessary not only to ensure a correct final diagnosis, but also to compare future studies. This will allow development of a clear algorithm to choose the best diagnostic and treatment strategy for every single and specific patient.

To conclude, strong evidence on the specificity and sensitivity of diagnostic modalities in patients presenting with ampullary tumors is missing. This systematic review concludes that a wide variety of modalities is used, whereby EUS ad IDUS demonstrate the best outcome regarding differentiation between benign and malignant ampullary tumors. Based on the current study, it is not possible to conclude whether this should be combined with a biopsy or another diagnostic modality.

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Supplementary material

A. Search in PubMed

((((((((("Ampulla of Vater"[Mesh]) OR (Vater ampulla)) OR (Ampulla of vater)) OR (Ampullary)) OR (Hepatopancreatic ampulla)) OR (Vater* ampulla)) OR (Major duodenal papilla)) OR (Greater duodenal papilla)) AND (((((((("Neoplasms"[Mesh]) OR ("Common Bile Duct Neoplasms"[Mesh])) OR (Neoplas*)) OR (Tumor*)) OR (Tumour*)) OR (Cancer*)) OR (Malignan*)) OR (Carcinom*))) AND ((((((((((((((((((("Magnetic Resonance Imaging"[Mesh]) OR ("Ultrasonography"[Mesh])) OR ("Endoscopy, Digestive System"[Mesh])) OR ("Tomography, X-Ray Computed"[Mesh])) OR (Transabdominal ultrasound)) OR (CT scan)) OR (CT)) OR (Computed tomography)) OR (MRI)) OR (Magnetic resonance imaging)) OR (Magnetic resonance cholangiopancreatography)) OR (MRCP)) OR (Endoscopic ultrasound)) OR (EUS)) OR (Endoscopic retrograde cholangiopancreatography)) OR (ERCP)) OR (Endoscopy)) OR (Duodenoscopy)) OR ("Radionuclide Imaging"[Mesh])) OR (pet ct)) OR (nuclear scintigraphy))) AND (((((("Biopsy"[Mesh]) OR (biopsy)) OR (Surgical biopsy)) OR (Endoscopic biopsy)) OR (Cytology))

B. Search in CINAHL

#	Query	Results
S1	(MH "Magnetic Resonance Imaging")	126,550
S2	(MH "Ultrasonopgrahy+") OR (MH "Endosonography")	104,216
S3	(MH "Endoscopy, Digestive System+")	27,849
S4	(MH "Tomography, X-ray Computed+")	109,718
S5	(MH "Cholangiopancreatography, Endoscopic Retrograde")	4,176
S6	transabdominal ultrasound	437
S7	ct scan	46,267
S8	computed tomography	150,525
S9	MRI	85,895
S10	magnetic resnonace imaging	144,829
S11	magnetic resonance cholangiopancreatography	446
S12	MRCP	506
S13	ERCP	3,446
S14	endoscopic retrograde cholangiopancreatography	4,706
S15	endoscopic ultrasound	4,419
S16	EUS	2,991
S17	Endoscopy	37,570
S18	Duodenoscope	257
S19	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18	414,067
S20	(MH "Biopsy+")	47,714
S21	Biopsy	78,361
S22	surgical biopsy	1,651
S23	endoscopic biopsy	980
S24	Cytology	6,873
S25	S20 or S21 or S22 or S23 or S24	83,378
S26	Ampulla of vater	208
S27	Ampullary	488
S28	Vater* ampulla	209
S29	Major duodenal papilla	44
S30	S26 or S27 or S28 or S29	687
S31	(MH "Duodenal Neoplasms")	676
S32	Neoplas*	494,148
S33	Tumor*	239,373
S34	Tumour*	30,251
S35	Cancer*	461,807
S36	Malignan*	76,543
S37	Carcinom*	111,884
S38	S31 or S32 or S33 or S34 or S35 or S36 or S37	736,452
S39	S19 AND S25 AND S30 AND S38	67

Limiters/Expanders: Expanders – Apply equivalent subjects; Serach modes – Boolean/Phrase
Last Run Via: Interfase – EBSCOhost Research Databases; Search Screen – Advanced Search; Database - CINAHL

C. Search in Cochrane

#1	MeSH descriptor: [Ampulla of Vater] explode all trees
#2	(Ampulla of vater):ti,ab,kw
#3	(Ampullary):ti,ab,kw
#4	("major duodenal papilla"):ti,ab,kw
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor [Duodenal Neplasms] explode all trees
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#8	(Tumor):ti,ab,kw
#9	(Tumour):ti,ab,kw
#10	(Cancer):ti,ab,kw
#11	(Carcinoma):ti,ab,kw
#12	(malignancy):ti,ab,kw
#13	#6 or #7 or #8 or #9 or #10 or #11 or #12
#14	#5 and #13
#15	MeSH descriptor: [Magnetic Resonance Imgaging] explode all trees
#16	MeSH descriptor: [Ultrasonography] explode all trees
#17	MeSH descriptor: [Endoscopy, Digestive System] explode all trees
#18	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#19	MeSH descriptor: [Cholangiopancreatography, Endoscopic Retrograde] explode all trees
#20	MeSH descriptor: [Endosonography] explode all trees
#21	("transabdominal ultrasonography"):ti,ab,kw
#22	(CT scan): ti,ab,kw
#23	("computed tomography scan"):ti,ab,kw
#24	("MRI scan"):ti,ab,kw
#25	("magnetic resonance imgaging"):ti,ab,kw
#26	("magnetic resonance cholangio-pancreatography"):ti,ab,kw
#27	(MRCP):ti,ab,kw
#28	(ERCP):ti,ab,kw
#29	("endoscopic retrograde cholangio-pancreatography"):ti,ab,kw
#30	(endoscpic ultrasound):ti,ab,kw
#31	("EUS"):ti,ab,kw
#32	("endoscope"):ti,ab,kw
#33	(duodenoscope):ti,ab,kw
#34	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#35	#14 and #34
#36	MeSH descriptor: [Biopsy] explode all trees
#37	("biopsy"):ti,ab,kw
#38	(surgical biopsy):ti,ab,kw
#39	(endoscopic biopsy):ti,ab,kw
#40	("cytology"):ti,ab,kw
#41	#36 or #37 or #38 or #39 or #40
#42	#35 and #41

D. Search in Embase

1.	exp Vater papilla carcinoma/ or exp ämpulla of Vater"/ or exp Vater papilla/
2.	Vater ampulla.mp.
3.	Ampulla of vater.mp.
4.	Ampullary.mp.
5.	Hepatopancreatic ampulla.mp.
6.	Vater* ampulla.mp.
7.	Hepatopancreatic duct.mp.
8.	1 or 2 or 3 or 4 or 5 or 6 or 7
9.	exp neoplasm/
10.	Neoplas*.tw.
11.	Tumor*.tw.
12.	Tumour*.tw.
13.	Cancer*.tw.
14.	Malignan*.tw.
15.	Carcinom*.tw.
16.	9 or 10 or 11 or 12 or 13 or 14 or 15
17.	8 and 16
18.	exp neuclear magnetic resonance imaging/
19.	exp echography/
20.	exp biliary tract endoscopy/ or exp digestive tract endoscopy/
21.	exp x-ray computed tomography
22.	exp endoscopic retrograde cholangiopancreatography/
23.	exp endoscopic ultrasonography/
24.	transabdominal ultrasound.mp.
25.	CT-scan.mp.
26.	CT.mp.
27.	Computed tomography.mp.
28.	MRI.mp.
29.	Magnetic resonance imaging.mp.
30.	Magnetic resonance cholangiopancreatography.mp.
31.	MRCP.mp.
32.	Endoscopic ultrasound.mp.
33.	EUS.mp.
34.	Endoscopic retrograde cholangiopancreatography.mp.
35.	ERCP.mp.
36.	Endoscopy.mp.
37.	Duodenoscopy.mp.
38.	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 of 31 or 32 or 33 or 34 or 35 or 36 or 37
39.	17 and 38
40.	exp endoscopic biopsy brush/ or exp endoscopic ultrasound guided fine needle biopsy/ or exp endoscopic biopsy/ or exp endoscopic biopsy needle/ or exp biopsy brush/
41.	Biop*.tw.
42.	Surigcal biop*.tw.
43.	Endoscopic biop*.tw.
44.	Cytology.tw.
45.	40 or 41 or 42 or 43 or 44
46.	39 and 45
47.	exp "sensitvity and specificity"/
48.	Accuracy.mp.
49.	Sensitivity.mp.
50.	Specificity.mp.
51.	Predictiv value*.mp.
52.	47 or 48 or 49 or 50 or 51
53.	46 and 52

CHAPTER 5

A population-based study on incidence, treatment, and survival in ampullary cancer in the Netherlands

Evelien J.M. de Jong, Sandra M.E. Geurts, Lydia G. van der Geest, Marc G. Besselink, Stefan A.W. Bouwense, Jeroen Buijsen, Cees H.C. Dejong, Lara R. Heij, Bas Groot Koerkamp, Ignace H.J.T. de Hingh, Chantal Hoge, Geert Kazemier, Hanneke W.M. van Laarhoven, Vincent E. de Meijer, Nadia Haj Mohammad, Marin Strijker, Karin C.A.A. Timmermans, Liselot B.J. Valkenburg-van Iersel, Johanna W. Wilmink, Vivianne C.G. Tjan-Heijnen, Judith de Vos-Geelen for the Dutch Pancreatic Cancer Group (DPCG)

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Abstract

Background
Ampullary cancer is rare and as a result epidemiological data are scarce. The aim of this population-based study was to determine the trends in incidence, treatment and overall survival (OS) in patients with ampullary adenocarcinoma in the Netherlands between 1989 and 2016.

Methods
Patients diagnosed with ampullary adenocarcinoma were identified from the Netherlands Cancer Registry. Incidence rates were age-adjusted to the European standard population. Trends in treatment and OS were studied over (7 years) period of diagnosis, using Kaplan-Meier and Cox regression analyses for OS and stratified by the presence of metastatic disease.

Results
In total, 3840 patients with ampullary adenocarcinoma were diagnosed of whom, 55.0% were male and 87.1% had non-metastatic disease. The incidence increased from 0.59 per 100,000 in 1989-1995 to 0.68 per 100,000 in 2010-2016. In non-metastatic disease, the resection rate increased from 49.5% in 1989-1995 to 63.9% in 2010-2016 ($p<0.001$). The rate of adjuvant therapy increased from 3.1% to 7.9%. In non-metastatic disease, five-year OS (95% CI) increased from 19.8% (16.9-22.8) in 1989-1995 to 29.1% (26.0-31.2) in 2010-2016 (logrank $p<0.001$). In patients with metastatic disease, median OS did not significantly improve (from 4.4 months (3.6-5.0) to 5.9 months (4.7-7.1); logrank $p=0.06$). Cancer treatment was an independent prognostic factor for OS among all patients.

Conclusion
Both incidence and OS of ampullary cancer increased from 1989 to 2016 which is most likely related to the observed increased resection rates and use of adjuvant therapy.

Introduction

Ampullary adenocarcinoma (hereafter: ampullary cancer), clustered in the group of periampullary cancers, is a rare cancer as it accounts for only 0.2% to 0.5% of all gastrointestinal tract tumors.[1-4] Population-based studies in the United States of America (USA, 1973-2005), France (1976-2009) and England (1998-2007) reported age-adjusted incidence rates in men and women of 0.46-0.63 and 0.30-0.40 per 100,000 persons, respectively.[5-7] Over the last decades, the incidence increased in the USA (+0.9% per year) and among men in France (+4.6% per year), but remained constant in England.[5-7]

In current practice, guidelines of distal biliary tract or pancreatic cancers are sometimes extrapolated to treat patients with ampullary cancer.[8-10] The standard of care for locoregional ampullary cancer is pancreato-duodenectomy.[2,3,10] Guidelines from the UK (2005), Belgium (2009), and the Netherlands (2011) recommend to restrain (neo-)adjuvant systemic or radiotherapy to study treatments, as the role of (neo-)adjuvant therapy in ampullary cancer is still debated.[9,11-20] Evidence is limited as most studies are retrospective and in clinical trials patients with ampullary cancer are often excluded.[13-21]

Longitudinal population-based analyses on ampullary cancer are limited.[5,7,22] To identify areas for improvement of survival, surgical and medical oncological treatment and counselling, it is essential to gain more insight in patient characteristics, therapies and outcomes in large population-based cohorts. Therefore, the aim of this study was to determine the trends in incidence, treatment and OS in patients diagnosed with ampullary cancer in the Netherlands between 1989 and 2016.

Methods

Database

The Netherlands Cancer Registry (NCR) is a population-based cancer registry in the Netherlands (17.4 million inhabitants; 2019). All patients with newly diagnosed malignancies are automatically identified through linkage to the national automated pathological archive (PALGA) and supplemented with data from the National Registry of Hospital Discharge Diagnosis (clinical diagnosis based on hospitalization, outpatient visits or imaging data). Trained administrators consult the medical records to verify the diagnosis and register information on diagnosis and treatment. Completeness of the NCR is estimated to be at least 95%.[23] This study was approved by the Scientific Committee of the Dutch Pancreatic Cancer

Group (DPCG) and the Privacy Review Board of the NCR. No approval from an ethics committee was required.[24]

Patients

All patients aged 18 years or older diagnosed with ampullary adenocarcinoma between 1989 and 2016 were identified from the NCR (International Classification of Disease for Oncology, third edition; C24.1 and morphology codes listed in Supplementary Table S5.1).[25] Tumor stage was registered according to the Union for International Cancer Control (UICC) TNM-classification valid at time of diagnosis.[26-28] The TNM classification for all patients was converted to TNM 7th edition (Supplementary Table S5.2). Tumor stage was based on pathological TNM-classification (pTNM). If missing, clinical TNM-classification (cTNM) was used. One digit Extent of Disease coding was recorded until 2012 for not microscopically verified malignancies (Supplementary Table S5.3). Patients with registered unknown metastatic disease status (MX) were categorised as no metastatic disease. Patients without any registered information on tumor classification, lymph node involvement and metastatic status were classified as 'unknown'. Patients were classified as M0 NOS (not otherwise specified) when patients had no metastatic disease, but could not be grouped based on tumor classification (TX) and/or lymph node involvement (NX). Two patients with a tumor without invasion and without lymph node involvement or metastases were excluded.

Treatment categories for patients with non-metastatic disease were: A) resection of the primary tumor (local surgical or endoscopic excision, pancreatoduodenectomy or not specified), B) resection of the primary tumor (local surgical or endoscopic excision, Whipple or pylorus preserving pancreatoduodenectomy or not specified) combined with (neo-)adjuvant chemo(radio)therapy, C) chemo- and/or radiotherapy alone, and D) no (anti-cancer) treatment (including surgical interventions, such as palliative bypass). Categories for patients with metastatic disease were: A) resection of the primary tumor and/or metastatic site(s) (location unknown), B) resection of the primary tumor combined with chemo(radio)therapy, C) chemotherapy alone, D) radiotherapy alone, and E) no (anti-cancer) treatment. One patient with no information on treatment was excluded.

OS was defined as time from date of diagnosis to date of death from any cause or censored at February 1st, 2019 or last follow-up date in case of emigration. Information on vital status was obtained through annual linkage of the NCR with the Municipal Administrative Database.

To evaluate trends in treatment and OS, four seven-year time periods of diagnosis were defined: 1989-1995, 1996-2002, 2003-2009, and 2010-2016.

Statistics

Annual incidence rates for the period 1989-2016 were calculated as number of new cases per 100,000 person-years, overall and stratified by sex. The incidence rates were age-standardised to the European standard population (ESP) from 1976 and to the revised ESP (RESP) from 2013. Change in incidence in 1989-2016 was evaluated by calculating the estimated annual percentage change (EAPC). Trends in treatment over time were analysed, stratified by metastatic disease status, using Chi-square test for trend. OS was calculated with the Kaplan-Meier method for the total study population and stratified by metastatic disease status and by resection within the group of patients with non-metastatic disease, using log rank tests for trend to compare OS between periods of diagnosis. Multivariable Cox regression analyses to assess the effect of period of diagnosis on OS were performed with and without treatment modality in all patients and in non-metastatic disease, adjusted for age, differentiation grade and TNM stage. Variables with a p-value <0.10 in the univariable regression analyses were selected for the multivariable regression analyses. In case of multicollinearity, the most relevant parameter to represent a certain variable family was selected based on the -2log likelihood. A p-value <0.05 was considered to be statistically significant. Data were analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armong, NY, USA).

Results

Of the 3840 patients included, median age at diagnosis was 72 years [IQR 63-79] and 55.0% of the patients were male (Table 5.1). The majority of the ampullary cancer cases were pathologically confirmed (89%). In total, 87.1% of the patients had non-metastatic disease, 12.1% had metastatic disease and in 0.9% (n=33) data were lacking. The median follow-up at last follow-up was 12.3 years.

Incidence rate

The incidence increased from 0.59 per 100,000 in 1989-1995 to 0.68 per 100,000 in 2010-2016. The overall incidence rate (ESR) was 0.66 per 100,000 between 1989 and 2016, with an estimated annual percentage of change (EAPC) of +0.63% (95% CI: 0.39-0.88) from 1989 to 2016 (ESP-based, p=0.02, Figure 5.1). The RESP-based incidence increased with a similar EAPC of +0.61 (Supplementary Figure S5.1). The increase in incidence was smaller in males than in females, with an EAPC of respectively +0.47% (ESP-based, p=0.13) and +0.68% (ESP-based, p=0.04).

Table 5.1 – Patient and tumor charactistics of patients diagnosed with ampullary cancer in the Netherlands in 1989-2016.

	Total (n = 3840)		**1989-1995 (n=785)**		**1996-2002 (n=834)**		**2003-2009 (n=1061)**		**2010-2016 (n=1160)**		**p-value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Sex											0.405
Male	2113	55	420	54	445	53	598	56	650	56	
Female	1727	45	365	47	389	47	463	44	510	44	
Age (median [IQR])	72 [63-79]		72 [63-80]		72 [63-79]		72 [62-79]		72 [64-79]		-
Age (categorical)											**0.033**
<65 years	1096	29	230	29	246	30	328	31	292	25	
65-75 years	1350	35	269	34	279	34	352	33	450	39	
≥75 years	1394	36	286	36	309	37	381	36	418	36	
T-classification*											**<0.001**
T1	948	25	224	29	240	29	277	26	207	18	
T2	719	19	120	15	121	15	199	19	279	24	
T3	835	22	153	20	202	24	216	20	264	23	
T4	224	6	0	0	0	0	83	8	141	12	
Unknown	1114	37	288	32	271	27	286	23	269	29	
N-classification*											**<0.001**
N0	1760	46	298	38	336	40	562	53	564	49	
N1	1108	29	147	19	195	23	296	28	470	41	
Nx	740	19	224	29	236	28	166	16	114	10	
Unknown	232	6	116	15	67	8	37	4	12	1	
M-classification											**<0.001**
M0	3344	87	709	90	735	88	913	86	987	85	
M1	463	12	56	71	88	11	146	14	173	15	
Unknown	33	1	20	3	11	1	2	0	0	0	
TNM stage											**<0.001**
Stage I	1195	31	261	33	274	33	345	33	315	27	
Stage II	1145	30	212	27	258	31	298	28	377	33	
Stage III	201	5	0	0	0	0	72	7	129	11	
M0 NOS	803	21	236	30	203	24	198	19	166	14	
Stage IV	463	12	56	7	88	11	146	14	173	15	
Unknown	33	1	20	3	11	1	2	0	0	0	
Grade											0.152
Well differentiated	321	8	84	11	73	9	72	7	92	8	
Moderately differentiated	1244	32	244	31	287	34	340	32	373	32	
Poorly differentiated	755	20	151	19	164	20	205	19	235	20	
Unknown‡	1520	40	306	39	310	37	444	42	460	40	

Abbreviations: NOS=not otherwise specified; IQR=interquartile range.

* Classification based on pathological classification, supplemented with clinical classification and extent of disease respectively.

‡ Grade of differentiation is unknown because this is not reported in the pathological specimen, or because the patient had no pathological diagnosis.

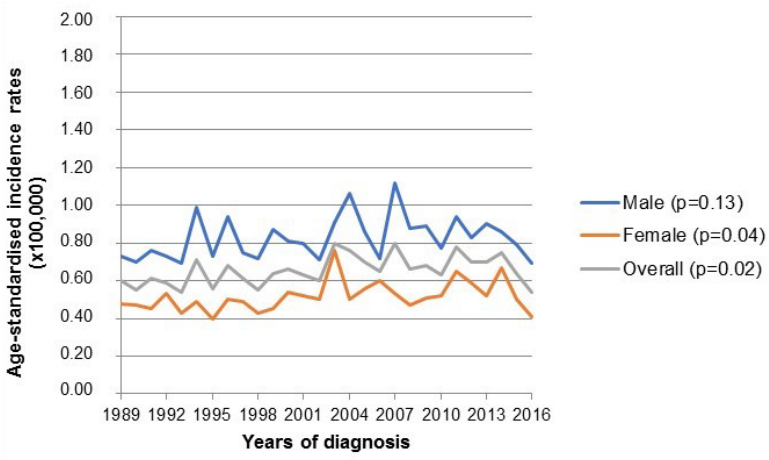


Figure 5.1 – Age-standardised incidence rates of ampullary cancer in the Netherlands between 1989 and 2016 based on the European standard population (p-value indicates significance of estimated annual percentage of change).

Trends in treatment

Of patients with non-metastatic disease (M0), the proportion of patients who underwent resection of the primary tumor without (neo-)adjuvant therapy increased over time from 49.5% in 1989-1995 to 63.9% in 2010-2016 (p<0.001, Figure 5.2A). Resection plus (neo-)adjuvant chemo(radio)therapy increased from 3.2% in 1989-1995 to 7.9% in 2010-2016 (p<0.001). The majority of the resected patients underwent a pancreatoduodenectomy and only a small proportion underwent endoscopic (n=17) or surgical local (n=22) resection (Supplementary Table S5.4). Within the group of (neo-)adjuvant therapy plus resection (n=157), 0.6% (n=1) received neoadjuvant radiotherapy, 75.8% received adjuvant chemotherapy, 3.1% adjuvant radiotherapy, and 20.3% adjuvant chemoradiotherapy between 1989 and 2016. No patients received neoadjuvant chemotherapy. Only few patients with non-metastatic disease received chemotherapy, radiotherapy, or chemoradiotherapy without resection of the primary tumor (n=27, 0.8% of all M0). Patients receiving no (anti-tumor) treatment decreased over time from 46.4% in 1989-1995 to 27.5% in 2010-2016 (p<0.001).

For patients with metastatic disease, chemotherapy use increased from 3.6% (n=2) in 1989-1995 to 28.3% (n=49) in 2010-2016 (p<0.001), while radiotherapy use remained nihil over time with none in 1989-1995 and 0.6% (n=1) in 2010-2016 (p=0.91), Figure 5.2B).

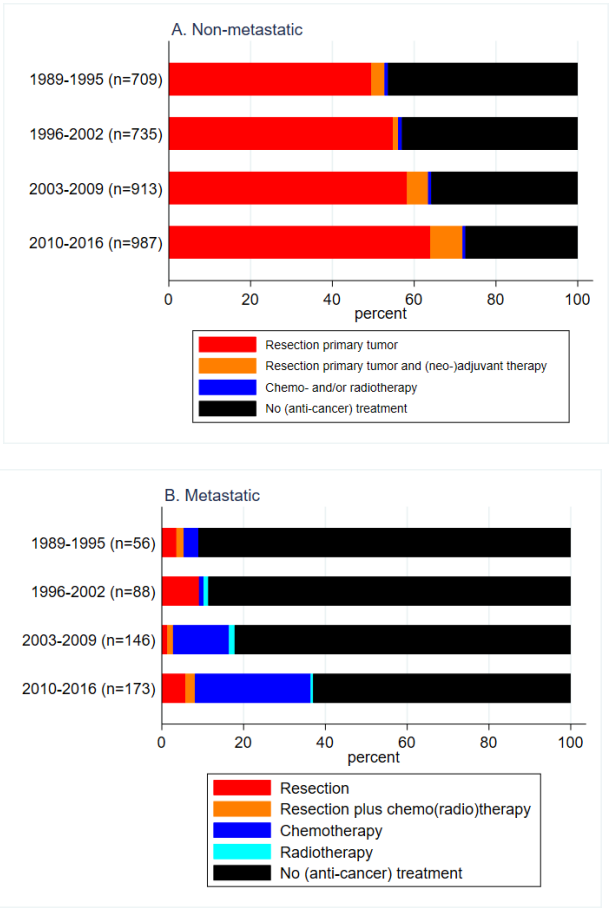


Figure 5.2 – Treatment of patients with (A) non-metastatic and (B) metastatic ampullary cancer in the Netherlands between 1989 and 2016.

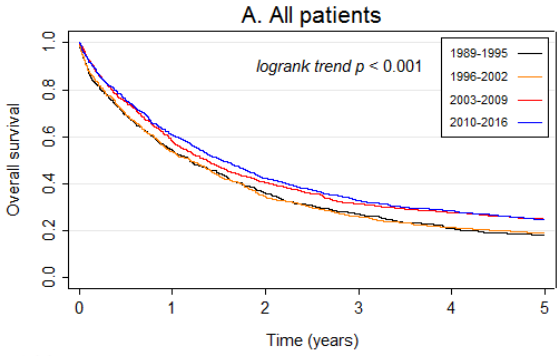
Trends in overall survival

Median OS of the total population was 16.1 months (95% CI 15.2-17.1) and increased over time from 14.2 months (95% CI 12.0-16.3) in 1989-1995 to 18.3 months (95% CI 16.4-20.2; p<0.001) in 2010-2016 (Figure 5.3A). Regardless of the period of diagnosis, median OS decreased with a more advanced TNM stage (Supplementary Figure S5.2).

In non-metastatic disease, 1- and 5-year OS increased from 58.3% (95% CI 54.6-61.9) and 19.8% (95% CI 16.9-22.8) in 1989-1995 to 67.3% (95% CI 64.3-70.2) and 29.1% (95% CI 26.0-32.1) in 2010-2016, respectively (logrank p<0.001, data not shown). Patients with non-metastatic disease who underwent resection had

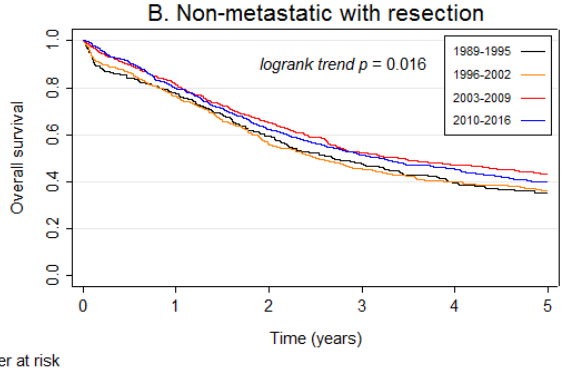
better OS compared to patients with non-metastatic disease without resection, a 5-year OS of 39.3% (95% CI 36.4-32.3) and 3.0% (95% CI 0.0-6.1) respectively (Figure 5.3B and 5.3C). In patients who also received (neo-)adjuvant therapy, the 5-year OS was 28.5% (95% CI 21.3-35.7). Multivariable Cox regression analyses showed that patient age, T- and N-classification and differentiation grade were prognostic factors for OS in non-metastatic ampullary cancer (Supplementary Table S5.5). In patients with metastatic disease, the median OS (95%) was 4.4 months (3.6-5.1) in 1989-1995 and 5.9 months (4.7-7.1) in 2010-2016 (logrank p=0.06, Figure 5.3D).

Better OS among all patients was observed after adjusting for period of diagnosis, age, sex, T- and N-classification and differentiation grade for patients diagnosed in 2003-2009 (HR=0.88, p=0.020), and 2010-2016 (HR=0.80, p<0.001) when compared with 1989-1995 (Table 5.2). After including treatment in the multivariable model, the period effects (expressed as HRs) on OS decreased and were no longer statistically significant.



Number at risk

1989-1995	785	425	283	211	164	142
1996-2002	834	447	288	217	177	157
2003-2009	1061	612	430	333	294	265
2010-2016	1160	705	489	342	248	163



Number at risk

1989-1995	374	290	222	177	147	131
1996-2002	412	315	231	187	162	148
2003-2009	579	469	378	303	274	251
2010-2016	709	565	440	326	239	157

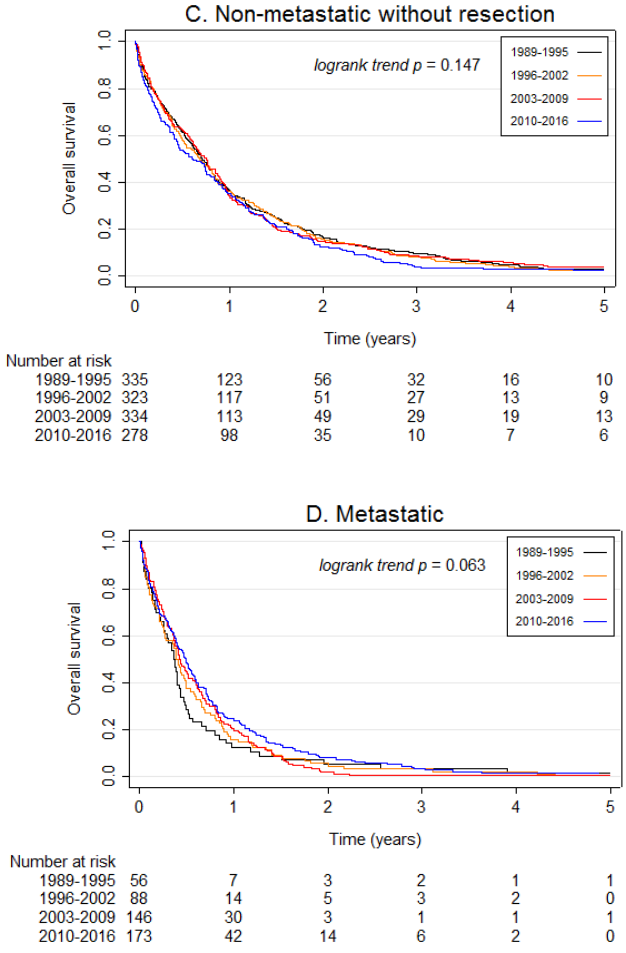


Figure 5.3 – Overall survival by period of diagnosis of (**A**) all, (**B**) non-metastatic resected, (**C**) non-metastatic non-resected, and (**D**) metastatic patients diagnosed with ampullary cancer in the Netherlands between 1989 and 2016.

Table 5.2 - Uni- and multivariable analysis for overall survival of patients with ampullary cancer with and without including treatment.

	N	Median survival in months (95%CI)	Univariable analysis		Multivariable analysis (without treatment)		Multivariable analysis (with treatment)	
			HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Period of diagnosis								
1989-1995	785	14.2 (12.0-16.3)	Ref.		Ref.		Ref.	
1996-2002	834	14.4 (12.5-16.4)	0.99 (0.90-1.10)	0.863	0.98 (0.88-1.08)	0.674	1.01 (0.92-1.12)	0.807
2003-2009	1061	16.4 (15.5-18.3)	0.85 (0.77-0.94)	**0.001**	0.88 (0.80-0.98)	**0.020**	0.94 (0.85-1.05)	0.261
2010-2016	1160	18.3 (16.4-20.2)	0.81 (0.74-0.90)	**<0.001**	0.80 (0.72-0.90)	**<0.001**	0.94 (0.84-1.05)	0.288
Age								
<65 years	1096	26.5 (23.7-29.3)	Ref.		Ref.		Ref.	
65-75 years	1350	17.6 (15.8-19.5)	1.39 (1.27-1.52)	**<0.001**	1.36 (1.24-1.48)	**<0.001**	1.27 (1.16-1.39)	**<0.001**
≥75 years	1394	10.1 (9.2-10.9)	2.35 (2.15-2.57)	**<0.001**	1.92 (1.73-2.12)	**<0.001**	1.34 (1.20-1.49)	**<0.001**
Sex								
Men	2113	16.2 (14.9-175)	Ref.		not included		not included	
Women	1727	15.8 (14.4-17.3)	0.99 (0.93-1.06)	0.785				
Differentiation grade								
Good	321	32.9 (26.4-39.4)	Ref.		Ref.		Ref.	
Moderate	1244	26.9 (24.2-29.6)	1.04 (0.91-1.19)	0.591	1.02 (0.89-1.17)	0.763	1.05 (0.92-1.21)	0.456
Poor or undifferentiated	755	13.3 (11.7-14.8)	1.61 (1.39-1.86)	**<0.001**	1.43 (1.23-1.65)	**<0.001**	1.40 (1.21-1.63)	**<0.001**
Unknown	1520	10.2 (9.4-11.0)	1.96 (1.72-2.24)	**<0.001**	1.30 (1.13-1.50)	**<0.001**	0.97 (0.84-1.12)	0.719
T-classification‡								
T1	948	26.4 (23.1-29.6)	Ref.		Ref.		Ref.	
T2	719	33.0 (28.0-37.9)	0.86 (0.77-0.97)	**0.010**	0.91 (0.81-1.02)	0.120	1.04 (0.92-1.16)	0.559
T3	835	19.5 (17.4-21.6)	1.30 (1.17-1.43)	**<0.001**	1.26 (1.13 (1.40)	**<0.001**	1.47 (1.32-1.65)	**<0.001**
T4	224	15.6 (13.4-17.8)	1.56 (1.33-1.83)	**<0.001**	1.49 (1.26-1.77)	**<0.001**	1.68 (1.41-2.00)	**<0.001**
Unknown	1114	6.8 (6.1-7.6)	3.31 (3.01-3.65)	**<0.001**	1.95 (1.74-2.18)	**<0.001**	1.19 (1.06-1.33)	**0.002**
N-classification‡								
N0	1760	26.6 (24.0-29.3)	Ref.		Ref.		Ref.	
N1	1108	17.5 (16.3-18.8)	1.48 (1.36-1.61)	**<0.001**	1.50 (1.37-1.64)	**<0.001**	1.67 (1.53-1.83)	**<0.001**
Nx	740	6.51 (5.61-7.41)	2.67 (2.43-2.92)	**<0.001**	1.49 (1.34-1.66)	**<0.001**	1.26 (1.14-1.40)	**<0.001**
Unknown	232	4.67 (3.64-5.69)	3.72 (3.23-4.29)	**<0.001**	1.20 (1.01-1.43)	**0.042**	1.25 (1.05-1.49)	**0.014**

Table 5.2 - (continued)

	N	Median survival in months (95%CI)	Univariable analysis		Multivariable analysis (without treatment)		Multivariable analysis (with treatment)	
			HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
M-classification								
M0	3344	19.5 (18.3-20.6)	Ref.		Ref.		Ref.	
M1	463	5.1 (4.6-5.6)	3.22 (2.91-3.57)	**<0.001**	2.46 (2.20-2.75)	**<0.001**	1.74 (1.55-1.96)	**<0.001**
Unknown*	33	0 (0.0-0.0)	5.14 (3.64-7.25)	**<0.001**	2.72 (1.87-3.95)	**<0.001**	1.40-2.96)	**<0.001**
Treatment								
No (anti-tumour) treatment	1632	6.6 (6.0-7.2)	Ref.		not included		Ref.	
Resection primary tumour	1940	35.8 (32.3-39.4)	0.23 (0.21-0.25)	**<0.001**			0.23 (0.20-0.26)	**<0.001**
Resection + chemo- and/or radiotherapy	164	30.0 (24.7-35.3)	0.28 (0.23-0.33)	**<0.001**			0.22 (0.18-0.27)	**<0.001**
Chemo- and/or radiotherapy	104	10.3 (8.4-12.0)	0.80 (0.66-0.98)	**0.030**			0.59 (0.48-0.73)	**<0.001**

Abbreviations: NOS=not otherwise specified; CI=confidence interval.

* 22 of 33 patients classified as unknown stage were diagnosed at autopsy, hence median OS was zero months.

‡ Variables were chosen to avoid multicollinearity between t/n-classification and TNM stage.

Discussion

This population-based study showed an increase in the incidence, resection rate and use of adjuvant therapy. Most importantly, 5-year OS improved from 19.8% in 1989-1995 to 29.1% in 2010-2016. In metastatic disease, chemotherapy was administered more often over time, but without any clinically relevant or statistically significant impact on OS. The multivariable analysis in all patients showed that the change in administered therapies could explain the improved OS over time.

In the present study, the incidence rates were higher compared with the ESR in England in 1998-2007.[7] Better diagnostic modalities over time and distinguishing ampullary cancer from other periampullary cancers more often probably explain the increase over time in the present study (+0.63%).[6,7]

Approximately 4% of all patients with non-metastatic disease in 1989-2016 received adjuvant chemo- and/or radiotherapy in the current study. This is lower than the 8.9% observed in France in 1976-2009 but appears to be in line with recommendations in the guidelines to limit the use to study treatments.[5] Also in the most recent time periods, patients with non-metastatic disease received adjuvant therapy less often (5.1% and 7.9% in 2003-2009 and 2010-2016, respectively) compared with a population-based study from the USA presenting an increase in use of adjuvant chemotherapy in resected ampullary cancer patients from 29% in 2004-2006 to 46% in 2010-2012.[22] Higher rates of adjuvant chemo(radio)therapy in ampullary cancer were also reported in retrospective single centre studies in the USA in 1977-2016.[29-32] Due to the small number of patients treated with surgery plus adjuvant therapy and the risk of confounding by indication, the benefit of adjuvant therapy on OS could not be assessed in this study. In a population-based study in the USA an improvement in survival (2004-2012) was seen in patients with surgically resected ampullary cancer, together with an increased use of adjuvant chemo(radio)therapy. The improved OS could mirror this increased use, but no analyses were done to confirm this association and the impact of other factors on OS.[22] Randomized controlled trials on adjuvant therapy, in which only limited numbers of patients with ampullary cancers are enrolled, report mixed results.[13,17,18] Regarding neoadjuvant therapy in ampullary cancer, only retrospective studies are available.[33-35] Therefore, the value of both neoadjuvant and adjuvant therapy in patients with ampullary cancer remains unknown and subject to further prospective studies. To obtain highest level of evidence on the efficacy of (neo)adjuvant therapy in patients with ampullary cancer in specific, a multi-centre prospective randomized controlled trial is needed. The provided results will contribute to evidence-based adaptations in international guidelines.

The multivariable analysis performed in all patients showed that the higher use of surgery (with or without (neo)adjuvant therapy) explained most of the improved OS over time. However, other factors might also explain the improved OS. First, a more accurate diagnosis of ampullary cancer, as diagnostic modalities got better over time, could have resulted in a better distinction between periampullary cancers. As the prognosis of ampullary cancer is better, compared with the periampullary cancers, a more homogeneous group results in a higher OS.[2,22,36] Second, advancement of both surgical techniques and postoperative support itself over time may have led to an increase in OS.[37,38] Third, improved surgical care and more expertise due to centralization and a minimal hospital volume requirement of pancreatic surgery, which was initiated in the 2000s and officially regulated from 2013 and onwards, might explain the improved outcome.[39] The effect of stage migration on OS is believed to be small as the increase in OS in patients with metastatic disease was not statistically significant over time.

The reported OS for the total population in the current study with one out of five patients alive after five years is comparable with the 27.7% and 20.8% in previously reported data from cohorts of France (1976-2009) and England (1998-2007), respectively.[5,7] On the contrary, the 5-year OS in patients with non-metastatic disease in the present study was lower compared to the OS data in the USA (5-year OS from 20% to 50%) between 2004 and 2012.[22] Possibly this could be explained by the inclusion of patients with unknown clinical or pathological staging, differences in selection of histologic subtypes, and differences in treatment.

Survival of patients with metastatic ampullary cancer in the present study remained poor. Our 1-year OS of 20% is lower compared with the 1-year OS of 44% in France (outcome for the total non-resected group) and approximately 38% in the USA.[5,6] Both the French and American study did not report patient characteristics and treatment modalities in detail hampering objective comparisons. Possibly the current cohort is contaminated with patients with other tumors originating around the pancreatic head as pathological confirmation of the diagnosis is often missing in metastatic disease. Furthermore, the increased use of chemotherapy did not seem to improve OS. This, however, should be interpreted with caution as the analysis was statistically underpowered with no more than 3% of the patients receiving chemotherapy. Although chemotherapy is not recommended in the Dutch guideline, clinicians might decide otherwise and prescribe chemotherapeutic agents approved for pancreatic and/or biliary tract cancer.

The current study has several limitations, inherent to the retrospective study design. First, data such as information on TNM stage, histological subtype (i.e., pancreatobiliary or intestinal type), time between diagnosis and treatment, the

presence of pre-existing comorbidities and recurrences, were partly missing, incomplete or could have been misclassified. Especially data on histological subtype would have been of extra value in survival analyses as these are prognostic factors.[3] Second, risk of residual confounding might explain part of the observed improvement in OS over time. Third, diagnosis of ampullary cancer is difficult, leading to presumed (radiological or histological) misclassification in both surgically and non-surgically treated patients.[36,40,41] It is expected that more patients with ampullary cancer are misclassified as other periampullary cancers than vice-versa, resulting in an underestimation of the true incidence and possibly distorted OS.

In conclusion, this population-based study showed a small increase in incidence and overall survival of patients with non-metastatic ampullary cancer over the last three decades in the Netherlands, among an expansion of applied surgery with and without (neo-)adjuvant chemotherapy in non-metastatic disease. Survival of patients with metastatic disease remained poor, despite higher proportions of patients being treated with chemotherapy in the more recent years.

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Supplementary material

Table S5.1 – Selected morphologies.

Code	Description
8000	Neoplasm, NOS
8001	Tumor cells
8010	Carcinoma, NOS
8011	Epithelioma
8012	Large cell carcinoma, NOS
8020	Carcinoma, undifferentiated, NOS
8021	Carcinoma, anaplastic, NOS
8022	Pleomorphic carcinoma
8031	Giant cell carcinoma
8032	Spindle cell carcinoma, NOS
8033	Pseudosarcomatous carcinoma
8035	Carcinoma with osteoclast-like giant cells
8046	Non-small cell carcinoma
8070	Squamous cell carcinoma, NOS
8082	Lymphoepithelial carcinoma
8140	Adenocarcinoma, NOS
8141	Scirrhous adenocarcinoma
8143	Superficial spreading adenocarcinoma
8144	Adenocarcinoma, intestinal type
8145	Carcinoma, diffuse type
8154	Mixed pancreatic endocrine and exocrine tumor
8160	Cholangiocarcinoma
8163	Pancreatobiliary neoplasm
8201	Cribriform carcinoma
8210	Adenocarcinoma in situ in adenomatous polyp
8211	Tubular adenocarcinoma
8255	Adenocarcinoma with mixed subtypes
8260	Papillary adenocarcinoma, NOS
8261	Adenocarcinoma in villous adenoma
8263	Adenocarcinoma in tubulovillous adenoma
8310	Clear cell adenocarcinoma, NOS
8430	Mucoepidermoid carcinoma
8440	Cystadenocarcinoma, NOS
8480	Mucinous adenocarcinoma
8481	Mucin-producing adenocarcinoma
8490	Signet ring cell carcinoma
8500	Ductal carcinoma, NOS
8510	Medullary carcinoma, NOS
8521	Infiltrating ductular carcinoma
8523	Infiltrating duct mixed with other types of carcinoma
8560	Adenosquamous carcinoma
8570	Adenocarcinoma with squamous metaplasia
8572	Adenocarcinoma with spindle cell metaplasia
8574	Adenocarcinoma with neuroendocrine differentiation
8575	Metaplastic carcinoma, NOS
8576	Hepatoid adenocarcinoma
9990	No microscopic confirmation

Table S5.2 – Conversion of TNM-classifications to a uniform classification based on the 7th edition.

T	N	M	TNM stage 4th and 5th edition	TNM stage 6th and 7th edition	TNM-classification used in this study
Tis	N0	M0	Stage 0	Stage 0	excluded
T1	N0	M0	Stage I	Stage IA	Stage I
T2	N0	M0	Stage II	Stage IB	Stage I
T3*	N0	M0	Stage II	Stage IIA	Stage II
T1	N1	M0	Stage III	Stage IIB	Stage II
T2	N1	M0	Stage III	Stage IIB	Stage II
T3*	N1	M0	Stage III	Stage IIB	Stage II
T4	Any N	M0	Stage IV	Stage III	Stage III
Any T	Any N	M1	Stage IV	Stage IV	Stage IV

* T4 tumors according to TNM edition 4 or 5 are registered as T3.

Table S5.3 – Conversion of extent of disease to TNM-classification used in this study.

Extent of disease	Explanation	TNM-classification used in this study
1	In situ tumor	Excluded
2	Localised tumor	Stage I
3	Regional tumor, direct extension only	M0 NOS (stage II/III)
4	Regional tumor, regional lymph nodes only	M0 NOS (stage II/III)
5	Regional tumor, direct extension and regional lymph nodes	M0 NOS (stage II/III)
6	Distant metastases	Stage IV
x	Unknown	M0 NOS

Table S5.4 – Type of resection in patients with non-metastatic ampullary cancer (n=2074) between 1989 and 2016.

Type of resection	Number of patients (%)
Local resection: endoscopic	17 (0.8)
Local resection: surgical	22 (1.1)
Local resection: unknown	5 (0.2)
Whipple/PPPD	1113 (53.7)
Unknown	917 (44.2)

Table S5.5 - Uni- and multivariable analysis for overall survival of patients with non-metastatic ampullary cancer with and without including treatment.

	N	5-year OS in % (95%CI)	Univariable analysis		Multivariable analysis (without treatment)		Multivariable analysis (with treatment)	
			HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Period of diagnosis								
1989-1995	709	19.8 (16.9-22.8)	Ref.		Ref.		Ref.	
1996-2002	735	21.4 (18.5-24.4)	0.97 (0.87-1.08)	0.571	0.97 (0.87-1.08)	0.561	1.00 (0.90-1.11)	0.976
2003-2009	913	28.9 (25.9-31.8)	0.81 (0.73-0.89)	**<0.001**	0.87 (0.78-0.98)	**0.020**	0.92 (0.82-1.03)	0.157
2010-2016	987	29.1 (26.0-32.1)	0.76 (0.68-0.85)	**<0.001**	0.80 (0.71-0.90)	**<0.001**	0.91 (0.81-1.03)	0.132
Age								
<65 years	953	38.7 (35.6-41.8)	Ref.		Ref.		Ref.	
65-75 years	1169	30.0 (27.3-32.7)	1.43 (1.30-1.58)	**<0.001**	1.41 (1.28-1.56)	**<0.001**	1.31 (1.19-1.45)	**<0.001**
≥75 years	1222	10.4 (8.6-12.2)	2.59 (2.35-2.85)	**<0.001**	1.95 (1.74-2.17)	**<0.001**	1.35 (1.20-1.52)	**<0.001**
Sex								
Men	1840	25.5 (23.5-27.6)	Ref.		not included		not included	
Women	1504	25.3 (23.0-27.5)	0.99 (0.92-1.07)	0.877				
T-classification								
T1	898	36.5 (33.4-39.7)	Ref.		Ref.		Ref.	
T2	662	41.3 (37.4-45.2)	0.83 (0.73-0.93)	**0.001**	0.87 (0.77-0.98)	**0.020**	1.01 (0.89-1.15)	0.859
T3	780	23.1 (20.0-26.1)	1.29 (1.16-1.44)	**<0.001**	1.22 (1.09-1.37)	**0.001**	1.45 (1.28-1.63)	**<0.001**
T4	201	19.4 (13.7-25.1)	1.55 (1.31-1.83)	**<0.001**	1.46 (1.22-1.75)	**<0.001**	1.69 (1.40-2.04)	**<0.001**
Unknown	803	3.2 (2.0-4.5)	3.24 (2.92-3.60)	**<0.001**	2.19 (1.93-2.49)	**<0.001**	1.21 (1.06-1.37)	**0.003**
N-classification								
N0	1641	37.6 (23.2-40.0)	Ref.		Ref.		Ref.	
N1	977	17.9 (15.4-20.4)	1.47 (1.35-1.61)	**<0.001**	1.56 (1.42-1.72)	**<0.001**	1.75 (1.59-1.93)	**<0.001**
Nx	576	8.6 (6.3-10.9)	2.59 (2.34-2.86)	**<0.001**	1.45 (1.28-1.63)	**<0.001**	1.24 (1.10-1.39)	**<0.001**
Unknown	150	1.5 (0.5-6.2)	3.53 (2.98-4.19)	**<0.001**	1.19 (0.97-1.46)	0.092	1.23 (1.00-1.50)	**0.047**
Differentiation grade								
Good	294	38.1 (32.3-43.8)	Ref.		Ref.		Ref.	
Moderate	1170	34.9 (32.1-37.7)	1.07 (0.93-1.24)	0.365	1.04 (0.90-1.24)	0.585	1.06 (0.92-1.23)	0.439
Poor or undifferentiated	644	19.6 (16.5-22.7)	1.56 (1.34-1.82)	**<0.001**	1.42 (1.22-1.67)	**<0.001**	1.39 (1.19-1.63)	**<0.001**
Unknown	1236	16.4 (14.3-18.4)	1.91 (1.66-2.20)	**<0.001**	1.29 (1.11-1.50)	**0.001**	0.96 (0.82-1.11)	0.555
Treatment								
No (anti-tumor) treatment	1243	3.0 (2.0-3.9)	Ref.		not included		Ref.	
Resection primary tumor	1917	40.1 (37.9-42.4)	0.25 (0.23-0.27)	**<0.001**			0.22 (0.19-0.25)	**<0.001**
Resection primary tumour + (neo-)adjuvant therapy	157	28.5 (21.3-35.7)	0.30 (0.25-0.36)	**<0.001**			0.21 (0.17-0.27)	**<0.001**
Chemo and/or radiotherapy	27	0.0 (0.0-0.0)	0.39 0.47-1.02)	0.061			0.57 (0.38-0.84)	**0.004**

Abbreviations: NOS=not otherwise specified; CI=confidence interval

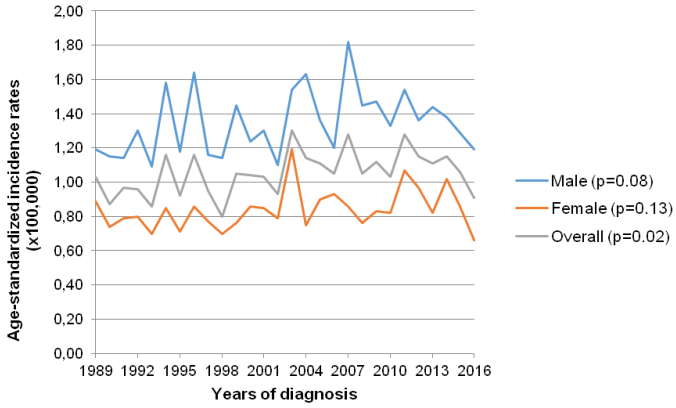
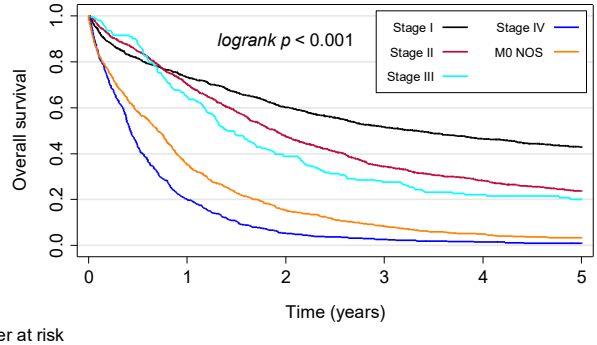


Figure S5.1 – Age-standardized incidence rates of ampullary cancer in the Netherlands between 1989 and 2016 based on the revised European standard population (p-value indicates significance of estimated annual percentage of change).



Number at risk

Stage I	1195	877	719	596	513	447
Stage II	1145	802	542	377	288	225
Stage III	201	130	78	52	38	27
Stage IV	463	93	25	12	6	2
M0 NOS	803	281	123	66	38	26

Figure S5.2 – Overall survival by TNM stage of patients with ampullary cancer in the Netherlands between 1989 and 2016. (NOS=not otherwise specified).

CHAPTER 6

Oncologic management of ampullary cancer: international survey among surgical and medical oncologists

Evelien J.M. de Jong, Daniel H.L. Lemmers, Andrea Benedetti Cacciaguerra, Stefan A.W. Bouwense, Sandra M.E. Geurts, Vivianne C.G. Tjan-Heijnen, Liselot B.J. Valkenburg-van Iersel, Johanna W. Wilmink, Marc G. Besselink, Mohammad Abu Hilal*, Judith de Vos-Geelen* for the Dutch Pancreatic Cancer Group (DPCG) and the International Study Group on Ampullary Cancer (ISGACA)
*Shared senior-authorship

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Abstract

Background
Ampullary adenocarcinoma (AC) is a rare neoplasm which as a result is lacking specific treatment guidelines. This international survey study was performed to gain insight in the current daily practice of AC.

Methods
Surgeons and medical oncologists, whom were members of the Dutch Pancreatic Cancer Group, International Study Group on Ampullary Cancer, International Hepato-Pancreato-Biliary Association, European and International Consortium on Minimally Invasive Pancreatic Surgery, or contributed to (peri)ampullary cancer research, were invited through email and newsletters between January and October 2021.

Results
Overall, 217 surgeons and medical oncologists completed the survey. Most of the respondents work in Europe (60%), and in a pancreatic expertise center (86%). The majority of respondents (87%) stated that the histological AC subtype (e.g. intestinal vs. pancreatobiliary) was determined in the resection specimen. Neoadjuvant treatment for resectable disease was considered by 24% and adjuvant therapy by 90% of the respondents, with 80% of them choosing adjuvant chemotherapy alone. The formation of multidisciplinary teams, improvement in resection procedures, increased availability of chemotherapy regimens, and increased knowledge on tumor biology were considered as the most important developments in the last five years. The necessity for randomized controlled trials was mentioned by 50% of the respondents.

Conclusions
This international survey highlights the existing variation in the management of patients with AC, especially regarding the use of (neo)adjuvant therapy. More data from trials and international registries are needed to develop evidence-based guidelines on surgical and oncological management with the ultimate aim to improve outcomes for patients with AC.

Introduction

Ampullary adenocarcinoma (AC) arises from the ampulla of Vater and accounts for less than 1% of all gastrointestinal malignancies and 7% of all periampullary cancers.[1-3] As a result, research into AC is limited and currently no specific guidelines on the surgical and oncological management are available. Hence, patients with AC are not seldomly treated according to guidelines for pancreatic, duodenal or biliary tract cancer.[4,5]

Radical surgical resection through pancreatoduodenectomy, which is considered one of the most complex intra-abdominal surgical procedures, is the only curative option for patients with AC.[6] Survival is relatively good, most likely due to the relatively early onset of symptoms and thereby low disease stage at presentation.[1,2,7]} The role of neoadjuvant and adjuvant therapy is still under debate. Data on chemo- and/or radiotherapy in AC are mostly derived from retrospective single-center studies or randomized controlled trials (RCTs) with a highly heterogeneous population, consisting of patients with other types of periampullary cancers and/or cancers from the biliary tract or duodenum.[8-11] Furthermore, most of these studies showed inconsistent results with low level of evidence. The optimal treatment strategy for patients diagnosed with metastatic AC is questioned for the same reasons.[8]

Clinicians may consult pancreatic or biliary tract cancer guidelines from the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), or the National Comprehensive Cancer Network (NCCN).[12-19] They might also consult national or institutional guidelines for the treatment of AC. As a result, a variation in therapeutic modalities for AC is expected worldwide.

To date, no studies have assessed the current international management strategies of patients diagnosed with AC. By gaining insight in the management and choices made by physicians, areas for further research and development can be identified, and a standardized approach can be developed with – in the end – improvement of survival as ultimate goal. Therefore, the purpose of this survey study is to assess the current international management of patients with AC and to study what factors influence the treatment strategies and counselling of patients with AC

Methods

Survey

An online survey was developed by the authors using Google Forms.(20) The questionnaire was divided into five topics regarding 1) background of the respondent, 2) diagnostic procedures to AC, 3) management of AC, 4) hypothetical scenarios, and 5) personal opinions on management of AC. The survey consisted of multiple-choice, checkbox and open questions. Most questions were mandatory. The survey itself is provided in the Supplementary Materials. The Medical Ethics Committee of Amsterdam UMC, Academic Medical Center location, reviewed this study and waived the need for additional ethical approval from the ethics committee, protocol number W20_497.

Respondents

The approached respondents were surgeons and medical oncologists involved in the management of patients with AC. Surgeons and medical oncologists were approached by email via the Dutch Pancreatic Cancer Group (DPCG), the International Study Group on Ampullary Cancer (ISGACA), the International Hepato-Pancreato-Biliary Association (IHPBA), the European and International Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS/I-MIPS), or identified through their contribution to one or more studies on (peri)ampullary cancer. They were invited by email and received a reminder after two to three weeks. In the invitation, respondents were asked to share the survey with their colleagues specialized in periampullary cancer. The link was also shared once on Twitter® by MAH and retweeted by MGB on March 1st 2021. By completing the survey, the respondents gave their informed consent. No incentives were offered. To have the opportunity to contact respondents for future studies, respondents were asked to fill in their email address at the start of the survey. This information was stored separately from the data collected.

Definitions

The countries where respondents work, were grouped as follows: Europe, North-America, South-America, Asia plus Oceania, and Africa. Respondents working in more than one institution were categorized in only one institution by using the following priorization: comprehensive cancer center, tertiary center, academic medical hospital/university hospital, teaching hospital, and non-teaching hospital.

Statistics

At the start, no formal sample size was calculated, we aimed to include a minimum number of 100 respondents. All completed surveys were analyzed. Results were reported for the total cohort. Categorical data were reported as numbers (percentages).

Results

Respondents

In total, 227 physicians completed the survey. Ten respondents were excluded from further analyses: five completed the survey twice (duplicates were removed from analysis) and five respondents were gastroenterologists or radiation-oncologists who are mainly involved in the diagnostic procedures or radiotherapy and to a lesser extent in the full width of the management of AC.

From the 217 respondents included for final analysis, 180 were surgeon (83%), and 37 were medical oncologist (17%; Table 6.1). Half of the respondents were involved in the management of patients diagnosed with AC for more than 10 years (56%). The majority of the respondents (86%) worked in a pancreatic cancer center. The respondents are employed in 47 different countries, of whom most of which 16% in the United States of America, 15% in Italy, and 12% in the Netherlands. Distributed per continent, the majority worked in Europe (60%), followed by Asia/Oceania (18%), North-America (17%), South-America (4%), and Africa (0.5%; Figure 6.1).

Diagnostic procedures

Endoscopic ultrasound is nearly always performed in patients suspected of AC according to 61% of the respondents, and endoscopic retrograde cholangiopancreatography in nearly all patients suspected of ampullary cancer with obstruction according to 73% of the respondents. A biopsy, irrespective of the procedure, is obtained prior to neoadjuvant treatment, surgery, and start of palliative treatment in nearly all of the patients by respectively 92%, 63%, and 84% of the respondents (Figure 6.2). Only 28 respondents (13%) stated that the histological subtype (e.g. intestinal vs. pancreatobiliary) is rarely or never determined in the resection specimen. According to 71% of all respondents, the assessment of the histological subtype is based on both morphological and immunohistochemical features.

After pathological assessment, 52% of the respondents reported that in >10% of the cases a preoperative diagnosis of AC had to be changed to another type of periampullary cancer. A change of the preoperative diagnosis of any other periampullary cancer to AC in >10% of the patients was reported by 30% of the respondents.

Table 6.1 – Background information of respondents (n=217).

	Number	**%**
Gender		
Male	179	82%
Female	38	18%
Age		
≤30 years	2	1%
31-45 years	112	52%
46-60 years	79	36%
>60 years or older	24	11%
Specialty		
Surgeon	180	83%
Medical oncologist	37	17%
Years involved in management of patients with AC		
≤10 years	95	44%
>10 years	122	56%
Continent		
Europe	131	60%
North-America	36	17%
South-America	9	4%
Asia/Oceania	40	18%
Africa	1	<1%
Institution		
Comprehensive cancer center	37	17%
Tertiary medical center	57	26%
Academic medical hospital/university hospital	88	41%
Teaching hospital	28	13%
Non-teaching hospital	7	3%
Pancreatic expertise center		
Yes	186	86%
No	31	14%
Number of patients diagnosed with AC annually in institution		
1-2 patients	17	8%
3-5 patients	59	27%
6-10 patients	57	26%
>10 patients	77	36%
Unknown	7	3%

Abbreviations: AC=ampullary adenocarcinoma.

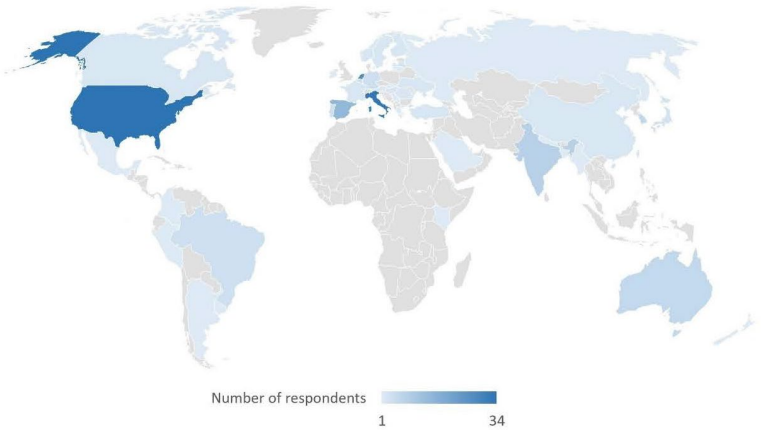

Figure 6.1 – Respondents per country.

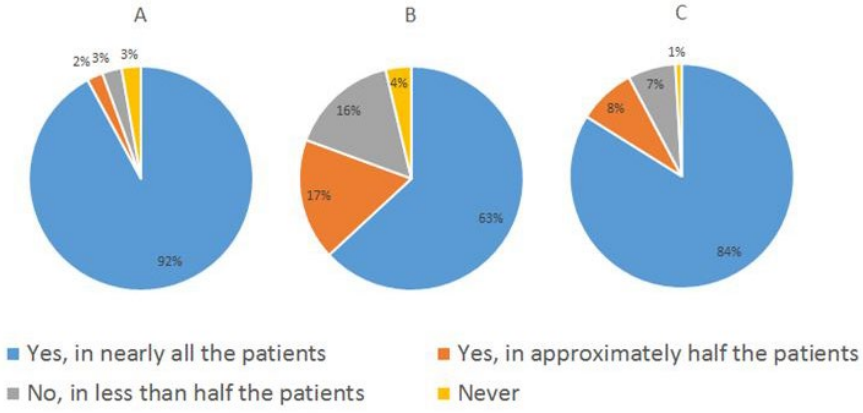

Figure 6.2 – Biopsy obtained prior to (**A**) neoadjuvant therapy, (**B**) resection, and (**C**) start of palliative treatment.

Management of ampullary cancer

In general, the majority of respondents take the patient's performance status (96%) and the presence of metastatic disease (93%) into consideration when choosing a treatment for patients with AC (Figure 3). Lymph node involvement (76%), resection margin (71%), tumor classification (69%), the preference of the patient (59%), age of the patient (58%), and histological subtype (56%) are also found to be important factors.

One or more guidelines were consulted during the management of AC by 142 respondents (65%). These included either the ASCO, ESMO, NCCN, a national or institutional guideline. The guidelines consulted are for pancreatic cancer (n=87; 61%), ampullary cancer (n=70; 49%), biliary tract cancer (n=62; 44%), and small bowel cancer (n=22; 15%). The majority of the respondents (82%) reported that nearly all patients' treatment strategies are discussed in a multidisciplinary team meeting.

Surgical management

Of all respondents, 56% reported that endoscopic and local transduodenal ampullectomy are performed in their center, mainly in patients with lymph node negative disease (88% of the respondents) and patients with a clinical AJCC tumor classification of T1 (91% of the respondents). Half of the respondents (55%) reported that over 40 pancreatoduodenectomies are performed in their center annually.

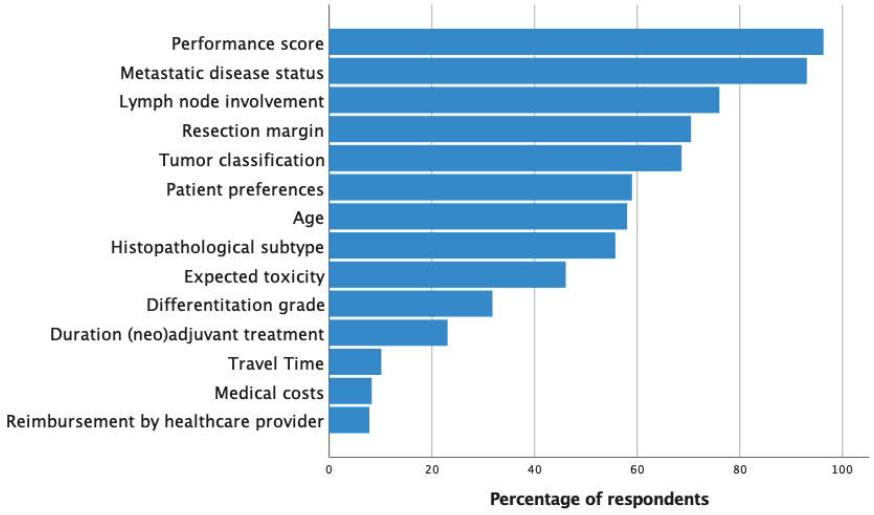

Figure 6.3 – Factors taken into consideration when choosing treatment for patients with ampullary cancer.

Neoadjuvant and adjuvant therapy

Neoadjuvant treatment is considered by 24% of correspondents, with 30% of these respondents opting for neoadjuvant treatment with (modified) fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). When selecting neoadjuvant therapy, 87% of the respondents take macrovascular invasion into consideration.

Adjuvant therapy after resection of AC was considered by 81% of the medical oncologists and 92% of the surgeons, with 80% choosing for adjuvant chemotherapy alone and 10% preferring combined chemoradiation. For the intestinal subtype, 33% of respondents prescribed (modified) FOLFIRINOX as adjuvant treatment, and 44% fluorouracil or capecitabine plus oxaliplatin (FOLFOX or CAPOX). Other adjuvant chemotherapeutic treatment regimens prescribed for the intestinal subtype are displayed in Figure 6.4. For the pancreatobiliary subtype, 51% of respondents prescribed (modified) FOLFIRINOX as adjuvant treatment, followed by 39% of respondents prescribing gemcitabine plus capecitabine (Figure 6.4).

When patients present with locally advanced AC, 45% of respondents consider neoadjuvant and adjuvant chemotherapy, 40% neoadjuvant chemotherapy only, 17% adjuvant chemotherapy only, and 12% neoadjuvant chemoradiation. Chemotherapeutic agents prescribed are (modified) FOLFIRINOX (73%), gemcitabine plus capecitabine (33%), gemcitabine plus cisplatin (32%), FOLFOX or CAPOX (31%), and/or gemcitabine monotherapy (14%).

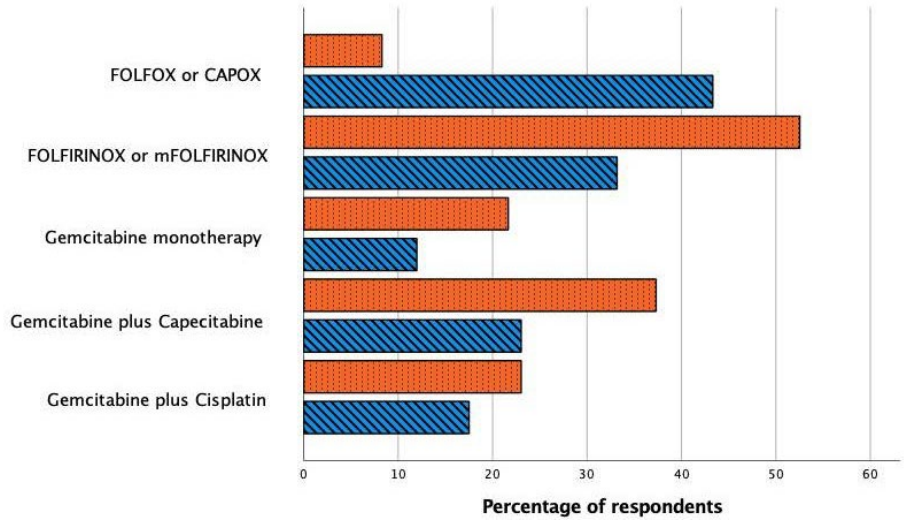

Figure 6.4 – Adjuvant therapy in intestinal (blue striped) and pancreatobiliary (orange dotted) subtype.

When patients present with metastatic AC, 98% of respondents would consider chemotherapeutic treatment. The regimens considered were (modified) FOLFIRINOX (55%), gemcitabine plus cisplatin (39%), FOLFOX or CAPOX (35%), gemcitabine plus capecitabine (29%), gemcitabine monotherapy (17%), and/or gemcitabine plus nab-paclitaxel (1%). Four respondents stated the choice for

certain chemotherapeutic regimens would depend on the histological subtype without specifying the difference in choice. Twelve surgeons stated they would refer the patient to the medical oncologist.

Future directions

The majority of the respondents (66%) were satisfied with the current treatment options. The formation of multidisciplinary teams, improvement in (minimally invasive) surgical procedures, possibilities of local (endoscopic) resection, increased availability of chemotherapy regimens, and the increased knowledge on histological subtype differentiation and tumor biology are reported as major improvements in the past five years. However, the necessity for randomized controlled trials and prospective studies on neoadjuvant and adjuvant chemo(radio)therapy was mentioned in 50% of the respondents. In these studies, histological subtype, but also molecular profiling should be taken into account as respondents suggest to ideally aim for a tailored treatment approach. In addition, setting up (inter)national registries of patients diagnosed with (peri)ampullary cancer was mentioned by 3% of the respondents.

Discussion

This survey with 217 respondents showed a considerable international variation in the treatment of AC. Before treatment for AC is started, pathological assessment is performed in the majority of the patients, providing the opportunity to differentiate treatment between histological subtypes. Still, the diagnosis based on the preoperative biopsy might be incorrect and examination of the resected specimen often results in alteration of the initial diagnosis (i.e. ampullary vs. other periampullary cancers). While neoadjuvant therapy is considered by only 23% of respondents, 90% of the respondents consider adjuvant therapy, where a great variation was seen in chemotherapeutic agents prescribed. When choosing an adjuvant chemotherapy regimen, half of the respondents take the histological subtype into consideration.

As this is the first survey on the international management of AC, we cannot compare our results to other studies. The complex anatomy of the periampullary region challenges the diagnosis of the origin of the tumor and only pathological assessment of the resection specimen can be conclusive. The majority of our respondents mentioned that a biopsy is obtained prior to the start of therapy. Yet, 52% of the respondents stated that in at least 10% of patients diagnosed with AC, the initial diagnosis had to be altered from ampullary to periampullary and 30% of

the respondents reported an alteration from periampullary to ampullary in >10% of the patients. This is in line with van Roessel et al. who reported that 16% of all patients who underwent a pancreatoduodenectomy for AC were preoperatively misdiagnosed.[21] The positive predictive value of a preoperative diagnosis of ampullary cancer was 73%. This indicates that pathological assessment of the resected AC specimen currently is the gold standard in the final disease characterization and determining its histopathological subtypes. Final disease characterization and determining the histologic subtypes of the tumor for indication of neoadjuvant or palliative treatment remains therefore difficult as the diagnosis can only be based on a biopsy.

In addition, pathological assessment of the tumor is of great importance to differentiate between the histological subtypes: intestinal vs. pancreatobiliary type. The subtype is related to the tumor behaviour and also affects therapy effectiveness.[22,23] In a retrospective propensity-score matched cohort, Moekotte et al. showed that gemcitabine-based adjuvant therapy led to an improved overall survival in patients with the pancreatobiliary subtype, but not in patients with the intestinal subtype.[24] Patients with the intestinal subtype might benefit more from adjuvant chemotherapeutic agents used in colorectal and small bowel cancer types, such as FOLFOX and CAPOX. But no studies have confirmed this yet. Therefore pathology assessment of the histological subtype should be done in every patient. Techniques other than morphological and immunohistochemical staining, e.g., the use of genetic and/or protein biomarkers, might be used in the future to improve the pathological diagnosis of the tumor origin and histological subtype, or as predictive biomarker.[25,26]

Interestingly, although no international guidelines specifically focus on patients diagnosed with AC, 49% of the respondents reported to consult a guideline specific for AC, thus suggesting that either national or institutional guidelines have been developed, or that clinicians still consider and treat AC as pancreatic or distal bile duct cancers. Importantly, physicians should be aware that the level of evidence of the recommendations within the guidelines is low for patients diagnosed with AC, which highlights the need for further research and development of international guidelines on treatment modalities for AC.[12-19]

Approximately half of the respondent's state that endoscopic or local transduodenal ampullectomy are performed. Previous studies have shown that endoscopic and surgical local resection should only be performed in selected cases with benign tumors or premalignant tumors.[27-29] Local resection in patients with clinical T1 ampullary cancer without clinical signs of lymph node involvement might not be the adequate management. Pancreato-duodenectomy is the

treatment of choice when AC is deemed surgically resectable. As a result of technical developments, also laparoscopic and robot(assisted) pancreatoduodenectomy became available next to open pancreatoduodenectomy. However, the available studies on minimally invasive techniques for AC in specific are scarce and include small amounts of patients. Conclusive evidence on the superiority of laparoscopic or robot-assisted over open pancreatoduodenectomy is lacking. A recent single-center study among ampullary cancer patients, comparing laparoscopic with open pancreatoduodenectomy, including 103 patients (31 with laparoscopic pancreatoduodenectomy, and 72 with open pancreatoduodenectomy) showed a higher morbidity rate, but comparable mortality rates, stating laparoscopic procedures should only be performed in experienced centers.[30] Another retrospective study, however, showed no statistically significant difference in overall morbidity and mortality between laparoscopic or robot-assisted and open pancreatoduodenectomy.[31] Future studies, ideally randomized trials, are needed comparing open and minimally invasive pancreatoduodenectomy in order to study the true impact of minimally invasive techniques on mortality and morbidity for patients with AC.

The lack of high-level evidence and a standardized approach is confirmed by the variation in chemotherapeutic agents considered by the respondents. Only one randomized controlled trial in patients with periampullary cancers performed a underpowered subgroup analysis in patients diagnosed with AC (n=304) and showed no increase in survival with adjuvant 5-FU or adjuvant gemcitabine compared with observation (median survival: 57.1 months vs. 43.0 months; HR=0.78 (95% CI 0.61-1.18), p=0.32).[10] The chemotherapeutic agents currently considered by the respondents, such as (modified) FOLFIRINOX, gemcitabine plus capecitabine, and FOLFOX or CAPOX, all include a fluorouracil derivative and have been shown to be effective in one or more of the other periampullary cancers.[4,5]

Despite newly obtained evidence and the increased use of neoadjuvant chemo(radio)therapy in patients diagnosed with (borderline) resectable pancreatic cancer, the majority of the respondents do not consider this therapy for AC.[32,33] This might be explained by the rarity of AC and as a result the limited knowledge and evidence on the efficacy of neoadjuvant therapy in AC. Adjuvant therapy, on the contrary, is considered more frequently, despite the specialty of the respondents. The respondents preferred chemotherapy alone over (chemo)radiotherapy, resembling the pancreatic cancer and biliary tract cancer guidelines.[4,5] Reviews by Bonet et al. and Kwon et al. suggest, however, that chemoradiotherapy would be more beneficial than chemotherapy alone in

AC, mainly for patients with positive lymph nodes and tumor classification stage T3-T4.[34,35] Noteworthy, most studies included in these reviews are retrospective studies, or trials in which patients with AC are grouped with other periampullary cancers. Thus, the exact patient and tumor characteristics, such as lymph node involvement and perineural invasion, on which the choice for neoadjuvant and/or adjuvant therapy can be based, are still under debate.

The results obtained should be interpreted in light of several limitations. First, despite careful development of the survey, the questions could have been interpreted different by respondents. For instance regarding the use of specific guidelines for AC treatment. Second, the results are presented for respondents and not for centers. Multiple responders may have replied per center. Third, the majority of the respondents were surgeons, whom might have a different opinion regarding neoadjuvant and/or adjuvant therapy or specific chemotherapeutic options. Finally, despite several attempts we were not able to include more responders from developing countries to study the differences between developed and developing countries. This is probably the result of the approach of one Dutch consortium and the network of the authors working in the Netherlands and Italy. The majority of the respondents are currently working in developed countries, in which financial constraints essentially do not exist. In developing countries we expect a lower use of adjuvant therapy. A strength of this study is the participation of both surgeons and medical oncologists, reflecting the multidisciplinary management of AC. In addition, the areas requiring further investigation were not only identified by the results of the survey, but also acknowledged by the comments of the respondents. This confirms the quality of our survey.

Two third of the respondents were satisfied with the current management possibilities of AC and respondents reported an increment of studies on the effectiveness of chemotherapeutic agents (i.e. gemcitabine plus capecitabine, and FOLFIRINOX) in pancreatic cancer became available which are, despite the lack of evidence for AC specifically, extrapolated. Yet, the call for more evidence-based treatment strategies remains high. To obtain this evidence, international collaboration in randomized controlled trials or international registries are needed due to the low incidence of AC. In addition, respondents and literature show the importance of the assessment of histological subtype. International consensus by pathologists on how to diagnose AC and on criteria to differentiate between histological subtypes should be reached.

This international survey study highlights the worldwide variation in the management of patients diagnosed with AC, especially regarding (neo)adjuvant

therapy. In addition, respondents mention that patients with the pancreatobiliary subtype and patients with the intestinal subtype should be approached as two different groups. Surgeons and medical oncologists suggest to invest in multicenter randomized controlled trials and international registries. This way, evidence-based guidelines could be developed for a more standardized surgical and oncological management, thus improving the outcomes of patients with AC.

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Supplementary material

A. Survey

Dear Sir/Madam,

Thank you for participating in our survey study on ampullary cancer. This study aims to gain insight in the current daily practice on treatment strategies, to identify areas for further studies and to develop a standardized approach. If you are interested in (participating in) our future studies on ampullary cancer, you can let us know at the end of the survey.

Privacy: you will be asked to fill in your email address at the start of the survey. This in order to send reminders to those who have not filled in our survey yet and to get in contact with those who are interested in future studies. Prior to analyzing the results, email addresses will be stored separately from the given answers.

Informed-consent: by completing and sending the survey, the respondent accepts that his/her answers will be used in our research.

Background information

1. Gender
    a. Male
    b. Female

2. What is your age?
    a. 30 years or younger
    b. 31-45 years old
    c. 46-60 years old
    d. 61 years or older

3. What is your specialty, or for what specialty are you in training?
    a. Surgeon
    b. Medical oncologist
    c. Other, please specify …

4. How many years of experience do you have as a specialist?
    a. Currently in training
    b. 5 years or less
    c. 6-10 years
    d. 11 years or more

5. In what institution are you currently working?
   a. Tertiary medical center
   b. Academic medical center
   c. Teaching hospital
   d. Non-teaching hospital
   e. Other, please specify …

6. In which country are you currently working?
   Option to choose all countries

7. Are you working in a pancreatic expertise center?
   a. Yes
   b. No

8. How many years of experience in the management of patients diagnosed with ampullary cancer do you have?
   a. 5 years or less
   b. 3-10 years
   c. 11 years or more

The diagnostic procedure of ampullary cancer

This section of the survey contains questions on the diagnostic procedure of ampullary cancer.

1. At your institution, is endoscopic ultrasound performed in patients suspicious for ampullary cancer?
   a. Yes, in nearly all the patients
   b. Yes, in approximately half of the patients
   c. No, in less than half of the patients
   d. Never

2. At your institution, is endoscopic retrograde cholangiopancreatography (ERCP) performed in patients suspected of ampullary cancer with obstruction?
   a. Yes, in nearly all the patients
   b. Yes, in approximately half of the patients
   c. No, in less than half of the patients
   d. Never

3. At your institution, will a biopsy be obtained for pathological assessment prior to neoadjuvant treatment?
   a. Yes, in nearly all the patients
   b. Yes, in approximately half of the patients
   c. No, in less than half of the patients
   d. Never

4. At your institution, will a biopsy be obtained for pathological assessment prior to surgical resection?
   a. Yes, in nearly all the patients
   b. Yes, in approximately half of the patients
   c. No, in less than half of the patients
   d. Never

5. How often, after pathological assessment of the tumor tissue obtained via surgical resection, needs the preoperative diagnosis ampullary cancer to be adjusted to another type of periampullary cancer (pancreatic cancer/distal cholangiocarcinoma/duodenal adenocarcinoma)?
   a. ≤10%
   b. 10-20%
   c. 20-50%
   d. >50%
   e. Unknown

6. How often, after pathological assessment of the tumor tissue obtained via surgical resection, is the preoperative diagnosis pancreatic cancer/distal cholangiocarcinoma/duodenal adenocarcinoma be adjusted to ampullary cancer?
   a. ≤10%
   b. 10-20%
   c. 20-50%
   d. >50%
   e. Unknown

7. Is the histological subtype of ampullary cancer (e.g., intestinal or pancreobiliary or mixed) assessed by the pathologist?
   a. Always
   b. More often
   c. Rarely
   d. Never. You can skip the next question.

8. Is the histological subtype of ampullary cancer (e.g., intestinal or pancreatobiliary or mixed) assessed based on morphological or immunohistochemical features?
   a. Morphological features
   b. Immunohistochemical features
   c. Both morphological and immunohistochemical features
   d. Unknown
   e. Other, please specify ...

9. At your institution, will a biopsy be obtained for pathological assessment prior to starting palliative treatment?
   a. Yes, in nearly all the patients
   b. Yes, in approximately half of the patients
   c. No, in less than half of the patients
   d. Never

10. How do you register, in the electronic patient record, a patient with metastatic disease, with the primary tumor located in the ampulla of Vater?
    a. Ampullary cancer
    b. Distal cholangiocarcinoma
    c. Pancreatic cancer
    d. Duodenal adenocarcinoma
    e. Other, please specify …

The management of ampullary cancer

This section of the survey contains questions on guidelines, resection and chemotherapeutic agents.

1. How many patients are diagnosed with ampullary cancer at your institution on a yearly bias?
   a. 1-2 patients
   b. 3-5 patients
   c. 6-10 patients
   d. >10 patients
   e. Unknown

2. Do you consult one or more (inter)national guidelines during the management of a patient with ampullary cancer?
   a. Yes
   b. No, you can skip the next question.

3. From which organization do you consult the guideline(s)? More options can be selected.
   a. Institution/hospital you are working at
   b. National organization or cancer workgroup (from country you currently work)
   c. European Society for Medical Oncology (ESMO)
   d. National Comprehensive Cancer Network (NCCN)
   e. American Society of Clinical Oncology (ASCO)
   f. Other, please specify

4. Which guideline do you consult? More options can be selected
   a. Guideline for pancreatic cancer
   b. Guideline for biliary tract cancer
   c. Guideline for small bowel cancer
   d. Other, please specify

5. Are treatment strategies discussed in a multidisciplinary team?
   a. Yes, in (nearly) all patients
   b. Yes, in approximately half of the patients
   c. No, in less than half of the patients
   d. Never. You can skip the next two questions.

6. Do you deviate from the advice given by the multidisciplinary team without consulting one or more colleagues from the multidisciplinary team?
   a. Yes, please specify why in the next question.
   b. No, you can skip the next question.

7. Please specify when and/or why you deviate from the advice
   Open question

8. At your institution, are local resections (endoscopic or transduodenal) of ampullary cancer performed?
   a. Yes
   b. No, you can skip the next question.
   c. Unknown, you can skip the next question.
   9. What technique is used for local resection of the ampullary tumor?
   a. Endoscopic ampullectomy
   b. Local transduodenal ampullectomy
   c. Both
   d. Unknown

10. Are local resections (endoscopic or transduodenal) performed in patients with positive lymph nodes (at time of diagnosis)?
    a. Yes
    b. No
    c. Unknown

11. Are local resections (endoscopic or transduodenal) performed in patients with tumor classification T≥2 (at time of diagnosis)?
    a. Yes
    b. No
    c. Unknown

12. How many pancreatoduodenectomies are performed in your institution annually?
    a. ≤10
    b. 11-20
    c. 21-40
    d. 41-80
    e. ≥81
    f. Unknown

13. Do you consider neoadjuvant therapy in patients diagnosed with resectable ampullary cancer?
    a. Yes, chemotherapy only
    b. Yes, chemoradiation
    c. Yes, radiotherapy only
    d. No

14. What chemotherapeutic agent(s) do you prescribe in patients with resectable ampullary cancer as neoadjuvant therapy (more options can be selected)?
    a. Gemcitabine/cisplatin
    b. Gemcitabine/capecitabine
    c. Gemcitabine monotherapy
    d. FOLFIRINOX or mFOLFIRINOX
    e. FOLFOX or CAPOX
    f. None
    g. Other, please specify …

15. Do you consider adjuvant therapy after resection of ampullary cancer?
    a. Yes, chemotherapy only
    b. Yes, chemoradiation
    c. Yes, radiotherapy only
    d. No

16. What chemotherapeutic agent(s) do you prescribe in patients with resectable ampullary cancer, INTESTINAL subtype, as adjuvant therapy (more options can be selected)?
    a. Gemcitabine/cisplatin
    b. Gemcitabine/capecitabine
    c. Gemcitabine monotherapy
    d. FOLFIRINOX or mFOLFIRINOX
    e. FOLFOX or CAPOX
    f. None
    g. Other, please specify …

17. What chemotherapeutic agent(s) do you prescribe in patients with resectable ampullary cancer, PANCREATOBILIARY subtype, as adjuvant therapy (more options can be selected)?
    a. Gemcitabine/cisplatin
    b. Gemcitabine/capecitabine
    c. Gemcitabine monotherapy
    d. FOLFIRINOX or mFOLFIRINOX
    e. FOLFOX or CAPOX
    f. None
    g. Other, please specify …

18. What neoadjuvant and/or adjuvant therapy do you consider in patients diagnosed with locally advanced ampullary cancer (more options can be selected)?
    a. Neoadjuvant chemotherapy
    b. Adjuvant chemotherapy
    c. Neoadjuvant and adjuvant chemotherapy
    d. Neoadjuvant chemoradiation
    e. Adjuvant chemoradiation
    f. Neoadjuvant and adjuvant chemoradiation
    g. Neoadjuvant radiotherapy. You can skip the next question.
    h. Adjuvant radiotherapy. You can skip the next question.
    i. Neoadjuvant and adjuvant radiotherapy. You can skip the next question.
    j. None. You can skip the next question.

19. What chemotherapeutic agent(s) would you prescribe in patients with locally advanced ampullary cancer (more options can be selected)?
    a. Gemcitabine/cisplatin
    b. Gemcitabine/capecitabine
    c. Gemcitabine monotherapy
    d. FOLFIRINOX or mFOLFIRINOX
    e. FOLFOX or CAPOX
    f. None
    g. Other, please specify …

20. What chemotherapeutic agent(s) would you prescribe in patients with metastatic cancer with suspected ampullary cancer as primary tumor (more options can be selected)?
    a. Gemcitabine/cisplatin
    b. Gemcitabine/capecitabine
    c. Gemcitabine monotherapy
    d. FOLFIRINOX or mFOLFIRINOX
    e. FOLFOX or CAPOX
    f. None
    g. Other, please specify …

21. Do you consider patients with ampullary cancer to participate in clinical trials regarding (neo)adjuvant chemotherapy?
    a. Yes
    b. No

22. Do you consider patients with ampullary cancer to participate in clinical trials regarding palliative chemotherapy?
    a. Yes
    b. No

23. What is the biggest challenge you experience in the management of patients with ampullary cancer?
    Open question

Hypothetical scenarios (vignettes)

In the following sections, two vignettes will be presented followed by questions on what management strategy you would choose.

1. Which of the factors below do you take into consideration when choosing a treatment choice for patients with ampullary cancer (more factors can be selected)?
    a. Performance status of patient at time of diagnosis
    b. Age of patient at time of diagnosis
    c. Tumor classification
    d. Lymph node involvement
    e. Metastatic disease status
    f. Histology subtype (e.g., intestinal or pancreatobiliary or mixed)
    g. Resection margin
    h. Differentiation grade
    i. Duration of possible (neo)adjuvant treatment
    j. Expected toxicity of systemic therapy
    k. Patient preferences
    l. Travel time to hospital
    m. Medical costs
    n. Reimbursement by health insurer
    o. Other, please specify …

2. When opting for neoadjuvant therapy, do you take vascular invasion into consideration?
    a. Yes
    b. No

Scenario 1
A 66-year old male patient with an extensive medical history got diagnosed with non-metastatic ampullary cancer. The patient is considered fit enough for surgery.

1. Would you consider neoadjuvant therapy?
   a. Yes, chemotherapy only
   b. Yes, chemoradiation
   c. Yes, radiotherapy only
   d. No, you can skip the two questions.

2. What chemotherapeutic agent(s) do you consider for this patient as neoadjuvant therapy?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

3. If this patient had no comorbidities, what chemotherapeutic agent(s) would you consider?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

Scenario 2
A 47-year-old female patient with no medical history was diagnosed with an ampullary tumor. CT scan images showed no evidence of metastatic disease. A metal stent was placed prior to surgery. Pathological assessment after surgical resection: TNM8 pT2N2M0, intestinal subtype, negative resection margin. Macroscopically no residual tumor was left.

1. Would you prescribe adjuvant chemo- and/or radiotherapy in this patient (TNM8 pT2N2M0 & R0 resection)?
   a. Yes, adjuvant chemotherapy
   b. Yes, adjuvant radiotherapy. You can skip the next question.
   c. Yes, adjuvant chemoradiation.
   d. None. You can skip the two questions.

2. What would you then prescribe as adjuvant chemotherapy?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

3. If case of a R1 resection, what would you prescribe as adjuvant chemotherapy?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

4. What would you prescribe as adjuvant chemotherapy when this patient was diagnosed with no lymph node involvement (N0)?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

Within 6 months after finishing adjuvant chemotherapy, this 47-year old patient developed omental, mesenteric and liver metastases.

5. What treatment modality would you consider?
   a. Systemic chemotherapy
   b. Radiotherapy
   c. Chemoradiation
   d. Best supportive care
   e. Other, please specify …

Your opinion on current and future management

1. Are you satisfied with the treatment options for patients with ampullary cancer in your hospital?
   a. Yes, you can skip the next question.
   b. No, please specify in the next question.
   c. No opinion. You can skip the next question.

2. If no, what would in your opinion be the treatment in an ideal world?
   Open question

3. What have been the major changes in treatment in the last 5 years?
   Open question

4. What was the most important change and what is the reason for this change?
   Open question

5. In. your opinion, we should aim for…
   a. Treatments differentiated for histological subtypes (e.g., intestinal vs. pancreatobiliary)
   b. A universal for both histological subtypes
   c. Other, please specify …

6. What would your ideal study (incl. research study question) be regarding the management of ampullary cancer patients?
   Open question

7. If you have questions or remarks regarding our survey, feel free to leave them here:
   Open question

Thank you and future contact!

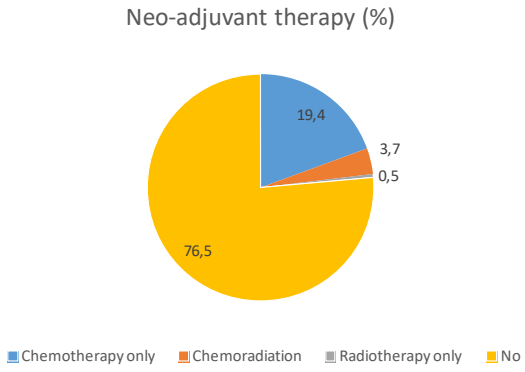
1. The results obtained by this survey will be used for future (prospective) studies on patients diagnosed with ampullary cancer. As stated previously, your email address will be stored separately from the answers given. Do you want to be contacted by the research team for (participating in) future studies on ampullary cancer?
   a. Yes
   b. No

B. Results of hypothetical scenarios

Scenario 1

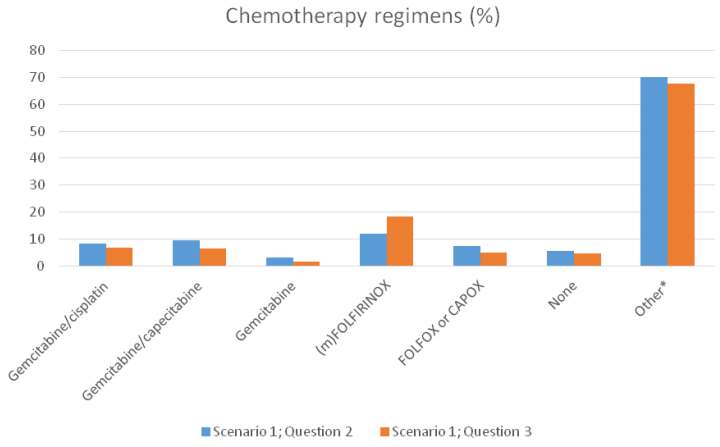
A 66-year-old male patient with an extensive medical history got diagnosed with non-metastatic ampullary cancer. The patient is considered fit enough for surgery.

1. Would you consider neo-adjuvant therapy?
   a. Yes, chemotherapy only
   b. Yes, chemoradiation
   c. Yes, radiotherapy only
   d. No, you can skip the two questions



2. What chemotherapeutic agent(s) do you consider for this patient as neo-adjuvant therapy?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

3. If this patient had no comorbidities, what chemotherapeutic agent(s) would you consider?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

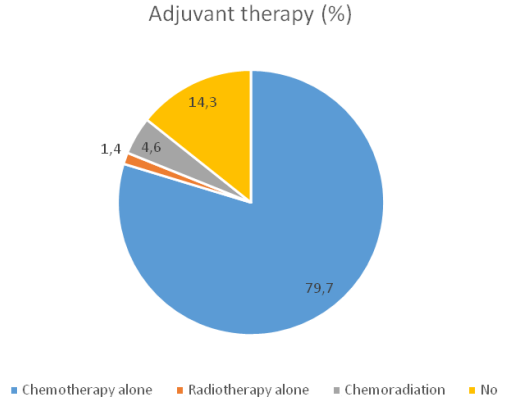


*Other:
Question 2 (with extensive medical history): not answered (68%), gemcitabine/nab-paclitaxel (0.1%), gemcitabine/cisplatin/S2 (0.05%), medical oncologists should decide (0.05%)
Question 3 (without comorbidities): not answered (64%), gemcitabine/nab-paclitaxel (0.1%), gemcitabine/cisplatin/S1 (0.1%), resection (0.05%), medical oncologists should decide (1.4%)

Scenario 2

A 47-year-old female patient with no medical history was diagnosed with an ampullary tumor. CT scan images showed no evidence of metastatic disease. A metal stent was placed prior to surgery. Pathological assessment after surgical resection: TNM8 pT2N2M0, intestinal subtype, negative resection margin. Macroscopically no residual tumor was left.

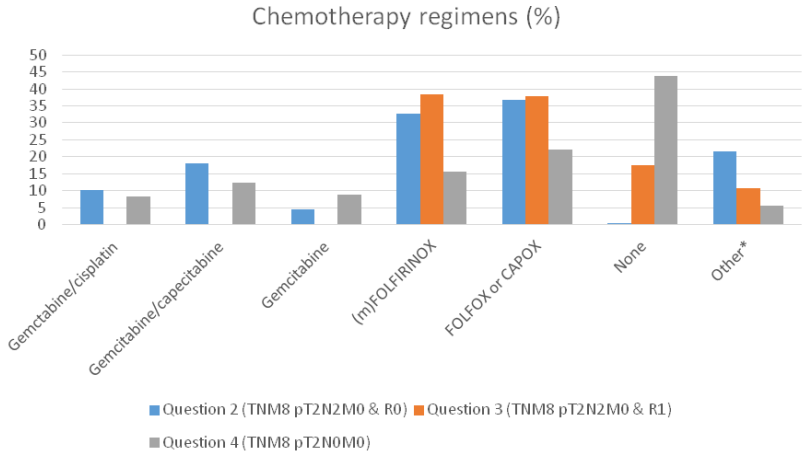
1. Would you prescribe adjuvant chemo- and/or radiotherapy in this patient (TNM8 pT2N2M0 & R0 resection)?
   a. Yes, adjuvant chemotherapy.
   b. Yes, adjuvant radiotherapy. You can skip the next question.
   c. Yes, adjuvant chemoradiation.
   d. None. You can skip the two questions.



2. What would you then prescribe as adjuvant chemotherapy?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

3. If case of a R1 resection, what would you prescribe as adjuvant chemotherapy?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …

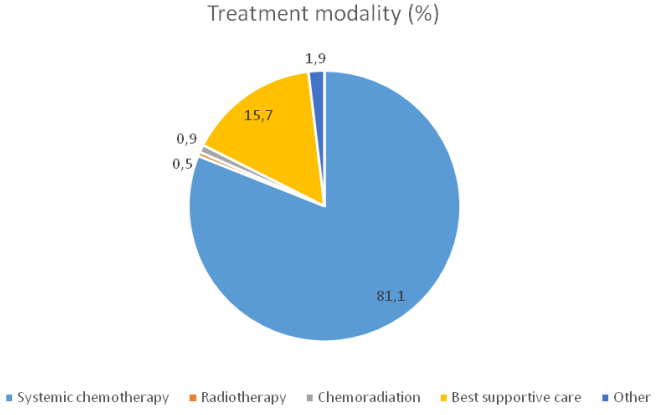
4. What would you prescribe as adjuvant chemotherapy when this patient was diagnosed with no lymph node involvement (N0)?
   a. Gemcitabine/cisplatin
   b. Gemcitabine/capecitabine
   c. Gemcitabine monotherapy
   d. FOLFIRINOX or mFOLFIRINOX
   e. FOLFOX or CAPOX
   f. None
   g. Other, please specify …



*Other:
Question 2 (TNM8 pT2N2M0 & R0): not answered (13%), capecitabine (2%), S1 (0.1%), chemotherapy and chemoradiation (0.05%), medical oncologists should decide (4%)
Question 3 (TNM8 pT2N2M0 & R1): capecitabine (1.8%), S1 (0.9%), depends on pathology (0.5%), radiotherapy (3%), re-operation (0.5%), medical oncologists should decide (4.1%)
Question 3 (TNM8 pT2N0M0): capecitabine (0.9%), S1 (0.5%), depends on T-sage and pathology (0.9%), medical oncologists should decide (3%)

Within 6 months after finishing adjuvant chemotherapy, this 47-year old patient developed omental, mesenteric and liver metastases.

4. What treatment modality would you consider?
   a. Systemic chemotherapy
   b. Radiotherapy
   c. Chemoradiation
   d. Best supportive care
   e. Other, please specify …



*Other:
Best supportive care (0.9%), chemotherapy based on mutational analysis (0.5%), second-line chemotherapy based on histologic subtype (0.5%)

PART III

Pancreatic ductal adenocarcinoma

CHAPTER 7

Real-world evidence of adjuvant gemcitabine plus capecitabine versus gemcitabine monotherapy for pancreatic ductal adenocarcinoma

Evelien J.M. de Jong*, Quisette P. Janssen*, Tessa F.A. Simons, Marc G. Besselink, Bert A. Bonsing, Stefan A.W. Bouwense, Sandra M.E. Geurts, Marjolein Y.V. Homs, Vincent E. de Meijer, Vivianne C.G. Tjan-Heijnen, Hanneke W.M. van Laarhoven, Liselot B.J. Valkenburg-van Iersel, Johanna W. Wilmink, Lydia G. van der Geest, Bas Groot Koerkamp**, Judith de Vos-Geelen**, for the Dutch Pancreatic Cancer Group
* Shared first authorship, ** Shared senior-authorship

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Abstract

Background
The added value of capecitabine to adjuvant gemcitabine monotherapy (GEM) in pancreatic ductal adenocarcinoma (PDAC) was shown by the ESPAC-4 trial. Real-world data on the effectiveness of gemcitabine plus capecitabine (GEMCAP), in patients ineligible for mFOLFIRINOX, are lacking. This study assessed whether adjuvant GEMCAP is superior to GEM in a nationwide cohort.

Methods
Patients treated with adjuvant GEMCAP or GEM after resection of PDAC without preoperative treatment were identified from the Netherlands Cancer Registry (2015-2019). The primary outcome was overall survival (OS), measured from start of chemotherapy. The treatment effect of GEMCAP vs. GEM was adjusted for sex, age, performance status, tumor size, lymph node involvement, resection margin, and tumor differentiation in a multivariable Cox regression analysis. Secondary outcome was the percentage of patients who completed the planned six adjuvant treatment cycles.

Results
Overall, 778 patients were included, of whom 21.1% received GEMCAP and 78.9% received GEM. The median OS was 31.4 months (95% CI 26.8-40.7) for GEMCAP and 22.1 months (95% CI 20.6-25.0) for GEM (HR 0.71, 95% CI 0.56-0.90; logrank p=0.004). After adjustment for prognostic factors, survival remained superior for patients treated with GEMCAP (HR=0.73, 95% CI 0.57-0.92, logrank p=0.009). Survival with GEMCAP was superior to GEM in most subgroups of prognostic factors. Adjuvant chemotherapy was completed in 69.5% of the patients treated with GEMCAP and 62.7% with GEM (p=0.11).

Conclusion
In this nationwide cohort of patients with PDAC, adjuvant GEMCAP was associated with superior survival as compared to GEM monotherapy and number of cycles was similar.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a common cause of cancer-related mortality among men and women worldwide, with a five-year overall survival (OS) of only 3%.[1,2] At time of diagnosis, the majority of the patients present with locally advanced or metastatic disease.[3] Only one fifth of the patients is able to undergo resection.[2,4] However, resection alone does not overcome the risk of local or distant recurrent disease in the majority of patients.[5]

A beneficial effect of adjuvant chemotherapy on the risk of recurrence and OS in PDAC was first shown by Oettle et al. in 2007.[6] Ever since, several randomized controlled trials have studied the efficacy of various adjuvant chemo-therapeutics in patients with PDAC who underwent resection.[7-11] For many years, gemcitabine monotherapy (GEM) has been the preferred adjuvant treatment in Western countries.[12, 13] Based on promising results in the metastatic setting, the use of combination therapies has emerged.[14-17] In 2017, the ESPAC-4 trial compared adjuvant gemcitabine plus capecitabine (GEMCAP) with GEM alone.[10] The median OS for patients treated with GEMCAP was 28.0 months compared with 25.5 months for patients treated with GEM (hazard ratio (HR): 0.82, 95% CI 0.68-0.98, p=0.032) with an acceptable level of treatment-related adverse events. The secondary analysis and long-term results confirmed the survival benefit as well as the decreased risk of developing local recurrence with GEMCAP treatment.[18, 19] In 2018, Conroy et al. showed the longest estimated survival thus far, with a median OS of 54.4 months in patients receiving adjuvant modified FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) compared with 35.0 months with GEM (HR=0.64, 95% CI 0.48-86, p=0.003).[11] This evident survival advantage came at the cost of increased chemotherapy-related adverse events in patients treated with modified FOLFIRINOX (mFOLFIRINOX). As a consequence, international guidelines recommend adjuvant mFOLFIRINOX only in patients with a good performance status.[12,20-22] In patients with impaired performance status, both adjuvant GEM and GEMCAP can be offered as alternative treatment. In the Netherlands, GEM was approved as adjuvant therapy in 2008 and recommended in the national guideline published in 2011.[23,24] In the 2019 guideline update, the option GEMCAP was added for patients unfit for mFOLFIRINOX.[20,25]

Evidence on the added value of capecitabine to adjuvant GEM monotherapy in PDAC is limited to the ESPAC-4 trial. Since clinical trial results cannot always be reproduced in real-world setting, this study aimed to assess whether adjuvant GEMCAP is associated with superior overall survival compared to adjuvant GEM in a Dutch nationwide cohort.

Methods

Data collection

This retrospective study used data from the nationwide Netherlands Cancer Registry (NCR). The NCR is a population-based registry including all patients with a newly diagnosed malignancy in the Netherlands since 1989, notified by the nationwide automated pathological archive (PALGA) and supplemented with the National Registry of Hospital Care (DHD-LBZ). Information on patient and tumor characteristics, treatment, and clinical outcomes are routinely extracted from the medical records using standardized definitions by trained administrators of the NCR. Patient characteristics included sex, age, performance status, and information on comorbidities according to the Charlson Comorbidity Index.[26] Tumor characteristics included the origin and morphology of the tumor classified according to the International Classification of Diseases for Oncology (ICD-O-3, pages 69-218), tumor size, number of positive lymph nodes, resection margin status (≥1 mm as R0), tumor differentiation grade, TNM-classification and corresponding disease stage.[27,28] For this study, the TNM-classification was converted to the 8th edition of the American Joint Committee on Cancer for all patients, using pathological tumor size and number of positive lymph nodes.[29] The definitions of pT1 and pT4 were identical between the 7th and 8th edition, and were therefore used for uniform staging. pT2 and pT3 definitions differed between both editions and thus staging of these tumors was based on tumor size according to the 8th edition. Treatment specifications included type and timing of surgery, number of cycles, and type of adjuvant treatment. Clinical outcomes included survival data, which was obtained by annual linkage with the nationwide Municipal Personal Records Database including the vital status of all Dutch inhabitants. Follow-up was completed until February 1st, 2021.[30]

Study population

For the current study, all patients aged ≥18 years with pancreatic ductal adenocarcinoma (ICD-O C25 excluding C25.4, see Supplementary Table S7.1 for morphology codes) diagnosed from 2015 to 2019 who underwent a resection were selected from the NCR. Additional inclusion criteria were treatment with adjuvant GEM monotherapy or adjuvant GEMCAP. All patients who received at least one cycle were included. Exclusion criteria were metastatic (stage IV) disease, a resection with macroscopic residual tumor (R2), neoadjuvant therapy, and adjuvant chemotherapy received outside of the Netherlands.

Treatment and outcome measures

The primary endpoint was OS, measured from start of chemotherapy until death from any cause. Patients alive at last follow-up were censored. Secondary endpoints included the annual number and proportion of patients receiving GEMCAP or GEM, the number of adjuvant chemotherapy cycles, the number of patients who switched to other adjuvant chemotherapy, and the percentage of patients who completed the planned six adjuvant treatment cycles.

Statistical analysis

Clinicopathologic characteristics were summarized for all patients and for GEMCAP and GEM separately. Data were presented as frequencies with proportions for categorical variables and median with interquartile range (IQR) for continuous variables. For categorical variables, the Chi-square test was used to compare the treatment groups as appropriate. For continuous variables, the Wilcoxon rank sum test was used. Median follow-up was calculated with the reverse Kaplan-Meier method. OS was estimated using the Kaplan-Meier method and difference in survival between the two treatment groups was analyzed using the log-rank test. In addition, univariable and multivariable Cox regression analyses were performed to assess the treatment effect expressed as HR with corresponding 95% CI, corrected for known and available prognostic factors (sex, age, WHO performance status, location, pathological tumor size, lymph nodes, resection margin, and tumor differentiation). Multiple imputation of missing data was performed using 25 imputed datasets with variable estimates obtained with the use of Rubin's rules. Imputation was performed for WHO performance status (n=279), tumor size (n=213), resection margin (n=20), and tumor differentiation (n=109). The proportional hazards assumption was assessed by visualization of Schoenfeld residuals and the log(-log(survival)) versus log of survival time graph. The proportional hazards assumption was not violated for any of the included variables. Results of the Cox regression analyses were presented as HR with 95% CI. Furthermore, the treatment effect of GEMCAP vs. GEM was assessed in prespecified subgroups using a Cox regression model with subgroups based on sex, age, WHO performance status, comorbidities, tumor location, stage, pathological tumor size, lymph nodes, resection margin, and tumor differentiation. Interaction was tested by adding the interaction term in the model with the p-value of the interaction term as indicator of possible interaction. The Chi-square test was used to compare the proportion of patients who completed at least six cycles of adjuvant chemotherapy and the proportion of patients who received three or less cycles of adjuvant chemotherapy between the two treatment groups. All tests were two-sided and values <0.05 were considered statistically significant. All analyses were performed using R software, version 3.4.3.

Results

The NCR database contained data on 1,992 patients who underwent resection for PDAC in the period 2015 to 2019. After applying the prespecified eligibility criteria, 778 patients were included, of whom 164 (21.1%) received adjuvant GEMCAP and 614 (78.9%) received adjuvant GEM (Figure 7.1). Fifty-four percent of the patients were male, the median age was 67 years (IQR 59-72), and 60.7% of the patients had WHO performance status 0 (Table 7.1). Most patients were diagnosed at stage II (41.0%), followed by stage III (36.5%), and stage I (22.5%). No statistically significant differences in characteristics were seen between treatment groups. Median time (IQR) from resection to start of adjuvant chemotherapy was 54.0 days (42.0-71.0) for patients treated with GEMCAP and 52.0 days (42.2-64.0) for patients treated with GEM (p=0.332).
The number of patients receiving GEM decreased and the administration of GEMCAP increased from 2015 to 2018, although the absolute number of patients receiving GEMCAP decreased in 2019 (Figure 7.2).

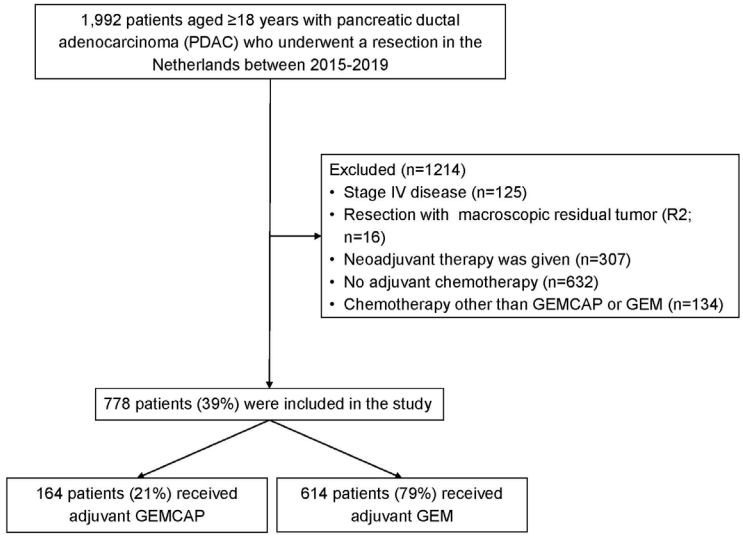

Figure 7.1 – Selection of the study population.
Abbreviations: GEM=gemcitabine monotherapy; GEMCAP=gemcitabine with capecitabine.

Table 7.1 – Baseline characteristics.

N	Overall 778	GEMCAP 164	GEM 614	P-value
Sex, n (%)				0.077
Male	420 (54.0)	78 (47.6)	342 (55.7)	
Female	358 (46.0)	86 (52.4)	272 (44.3)	
Age, years (median [IQR])	67.0 [59.0, 72.0]	66.0 [58.0, 71.0]	67.0 [60.0, 72.0]	0.118
WHO performance status, n (%)				0.455
WHO 0	303 (60.7)	62 (64.7)	241 (59.8)	
WHO 1	161 (32.3)	26 (27.1)	135 (33.5)	
WHO 2 - 3	35 (7.0)	8 (8.3)	27 (6.7)	
Concurrent conditions, n (%)				0.559
None	332 (48.2)	73 (50.7)	259 (47.5)	
Any	357 (51.8)	71 (49.3)	286 (52.5)	
Tumor location, n (%)				0.505
Other	148 (19.4)	34 (21.2)	114 (18.9)	
Head	615 (80.6)	126 (78.8)	489 (81.1)	
Type of resection, n (%)				0.452
Pancreatectomy	647 (84.6)	127 (83.6)	520 (84.8)	
Body / tail resection	110 (14.4)	22 (14.5)	88 (14.4)	
Total pancreatectomy	8 (1.0)	3 (2.0)	5 (0.8)	
Time to adjuvant chemo (days), (median [IQR])	52.0 [42.0, 64.8]	54.0 [42.0, 71.0]	52.0 [42.2, 64.0]	0.332
Pathological tumor stage*, n (%)				0.889
I	134 (22.5)	38 (23.9)	96 (22.0)	
II	244 (41.0)	64 (40.3)	180 (41.3)	
III	217 (36.5)	57 (35.8)	160 (36.7)	
Pathological tumor size, n (%)				0.156
<30 mm	245 (42.0)	75 (47.2)	170 (40.1)	
≥30 mm	338 (58.0)	84 (52.8)	254 (59.9)	
Lymph nodes, n (%)				0.912
Negative	199 (25.6)	43 (26.2)	156 (25.4)	
Positive	579 (74.4)	121 (73.8)	458 (74.6)	
Resection margin**, n (%)				0.054
R0	424 (55.9)	74 (48.7)	350 (57.8)	
R1	334 (44.1)	78 (51.3)	256 (42.2)	
Tumor differentiation, n (%)				0.086
Well	93 (13.9)	24 (16.9)	69 (13.1)	
Moderate	408 (61.0)	92 (64.8)	316 (60.0)	
Poor/Undifferentiated	168 (25.1)	26 (18.3)	142 (26.9)	

Abbreviations: GEM=gemcitabine; GEMCAP=gemcitabine with capecitabine; IQR=interquartile range; WHO=World Health Organization.

* Tumor stage according to AJCC 8th edition.

** 1mm definition of Royal College of Pathologists.

Percentage of missing data (overall/GEMCAP/GEM): sex (0%/0%/0%), age (0%/0%/0%), WHO performance status (36%/41%/34%), concurrent conditions (11%/24%/11%), location (2%/2%/2%), type of resection (2%/7%/0%), time to adjuvant chemo (0%/0%/0%), pathological tumor stage (24%/3%/29%), pathological tumor size (27%/1%/3%), lymph nodes (0%/0%/0%), resection margin (3%/7%/1%), tumor differentiation (14%/13%/14%).

Overall survival

The median follow-up time for patients alive at last follow-up was 33.5 months for patients treated with GEMCAP and 50.8 months for patients treated with GEM.

Median OS for patients treated with GEMCAP 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 GEM (unadjusted HR=0.71, 95% CI 0.56-0.90, p=0.004; Figure 7.3).

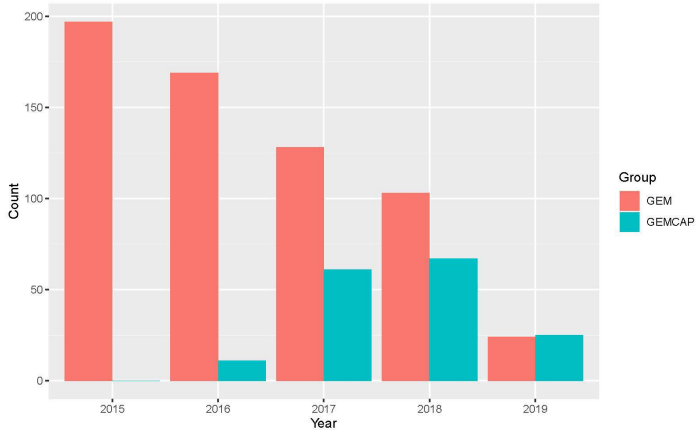

Figure 7.2 – Number of patients receiving gemcitabine with capecitabine (GEMCAP) or gemcitabine monotherapy (GEM) over time.

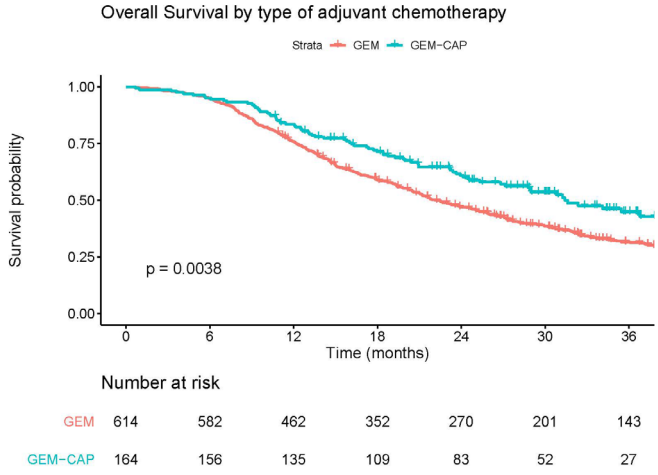

Figure 7.3 – Overall Survival, by type of adjuvant chemotherapy.
Hazard ratio for death: 0.71 (95% CI: 0.56 – 0.90), log-rank p=0.0038*.
Abbreviations: GEM=gemcitabine monotherapy; GEMCAP=gemcitabine with capecitabin.
* Significant interaction term of tumor location with adjuvant chemotherapy in unadjusted multivariable model including tumor location and adjuvant chemotherapy, p=0.02.

Univariable analyses showed that besides treatment, the location of the primary tumor, tumor size, lymph node involvement, resection margin, and tumor differentiation were all associated with OS (Table 7.2). Independent predictors of

survival were tumor size, lymph node involvement, resection margin, tumor differentiation, and treatment (GEM vs GEMCAP; HR=0.73, 95% CI 0.58-0.93, p=0.010).

Table 7.2 – Univariable and Multivariable Cox Regression Analysis of Overall Survival.

	Number of patients	Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Treatment					
GEM	614	1 [Reference]	1	1 [Reference]	1
GEMCAP	164	0.71 (0.56 – 0.90)	**0.004**	0.73 (0.58 – 0.93)	**0.010**
Sex					
Male	420	1 [Reference]	1	1 [Reference]	1
Female	358	0.97 (0.82 – 1.16)	0.767	0.98 (0.82 – 1.17)	0.810
Age					
<65 years	310	1 [Reference]	1	1 [Reference]	1
≥65 years	468	0.96 (0.79 – 1.16)	0.656	0.94 (0.79 – 1.13)	0.538
Performance status					
WHO 0	303	1 [Reference]	1	1 [Reference]	1
WHO 1	161	1.18 (0.95 – 1.46)	0.179	1.08 (0.87 – 1.35)	0.486
WHO 2 - 3	35	0.93 (0.58 – 1.50)	0.934	0.93 (0.58 – 1.49)	0.754
Tumor location					
Other	148	1 [Reference]	1	1 [Reference]	1
Head	615	1.29 (1.03 – 1.62)	**0.029**	1.25 (0.99 – 1.58)	0.062
Pathological tumor size					
<30 mm	245	1 [Reference]	1	1 [Reference]	1
≥30 mm	338	1.70 (1.39 – 2.09)	**<0.001**	1.54 (1.26– 1.89)	**<0.001**
Lymph nodes					
Negative	199	1 [Reference]	1	1 [Reference]	1
Positive	579	1.83 (1.48 – 2.27)	**<0.001**	1.56 (1.25 – 1.94)	**<0.001**
Resection margin					
R0	424	1 [Reference]	1	1 [Reference]	1
R1	334	1.44 (1.21 – 1.71)	**<0.001**	1.38 (1.15 – 1.65)	**<0.001**
Tumor differentiation					
Well	93	1 [Reference]	1	1 [Reference]	1
Moderate	408	1.57 (1.17 – 2.10)	**0.003**	1.50 (1.11 – 2.03)	**0.008**
Poor/Undifferentiated	168	2.35 (1.72 – 3.21)	**<0.001**	2.12 (1.54 – 2.93)	**<0.001**

Abbreviations: CI=confidence interval; GEM=gemcitabine; GEMCAP=gemcitabine with capecitabine; HR=hazard ratio; WHO=World Health Organization.
Imputation of missing data: sex (0%), age (0%), WHO performance status (36%), location (2%), pathological tumor size (27%), lymph nodes (0%), resection margin (3%), tumor differentiation (14%).

Subgroup analyses demonstrated comparable or superior survival with adjuvant GEMCAP in almost all subgroups (Figure 7.4). A significant interaction was found between tumor location and treatment (p=0.02), with a significant benefit of GEMCAP in patients with a tumor located in the pancreatic head (HR=0.65, 95% CI 0.50-0.85, p=0.002), but no significant benefit of GEMCAP in patients with a tumor located outside of the pancreatic head (HR=1.22, 95% CI 0.74-2.01, p=0.44). The positive effect of GEMCAP on OS was found in both patients with a positive resection margin (HR=0.70, 95% CI 0.51-0.97, p=0.034) and patients with a negative resection margin (HR=0.67, 95% CI 0.47-0.96, p=0.029).

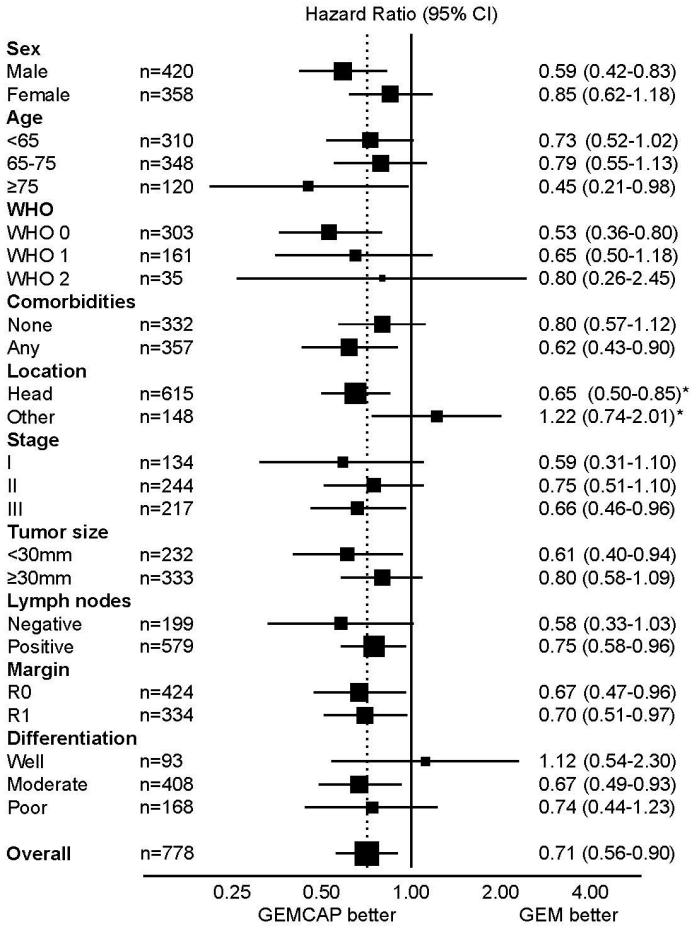

Figure 7.4 – Forest plot of the treatment effect on overall survival in prespecified subgroups.

Therapy

The proportion of patients completing six cycles of adjuvant chemotherapy was 69.5% in the GEMCAP group and 62.7% in the GEM group (p=0.11; Table 7.3). The proportion of patients receiving three or less cycles was 14.7% in the GEMCAP group and 21.4% in the GEM group (p=0.06).
Of the patients treated with GEMCAP, one patient switched to capecitabine monotherapy and five patients to gemcitabine monotherapy. Of the patients in the GEM group, one patient switched to GEMCAP, one patient to 5-FU and irinotecan, and four patients to capecitabine monotherapy as subsequent adjuvant therapy. One patient received tegafur/gimeracil/oteracil as third therapy after both gemcitabine and capecitabine monotherapy.

Table 7.3 – Number of completed chemotherapy cycles in patients treated with gemcitabine with capecitabine (GEMCAP) or gemcitabine (GEM)*.

Number of cycles (%)	Overall (n=778)	GEMCAP (n=164)	GEM (n=614)
>6	17 (2.2)	3 (1.8)	14 (2.3)
6	482 (62.0)	111 (67.7)	371 (60.4)
5	67 (8.6)	14 (8.5)	53 (8.6)
4	45 (5.8)	6 (3.7)	39 (6.4)
3	63 (8.1)	12 (7.3)	51 (8.3)
2	42 (5.4)	6 (3.7)	36 (5.9)
1	50 (6.4)	6 (3.7)	44 (7.2)
Unknown	12 (1.5)	6 (3.7)	6 (1.0)

* The proportion of patients who completed at least six chemotherapy cycles (p=0.11) and the proportion of patients who received three or less chemotherapy cycles (p=0.06) did not significantly differ between the two treatment groups.

Discussion

In this first nationwide study to compare adjuvant GEMCAP with adjuvant GEM in PDAC in daily clinical practice, adjuvant chemotherapy with GEMCAP was associated with a significantly prolonged OS compared with GEM monotherapy (median OS GEMCAP vs. GEM: 31.4 vs. 22.1 months; HR=0.71, 95% CI 0.56-0.90, p=0.004). This survival benefit persisted after adjustment for known prognostic factors in a multivariable Cox regression analysis and was consistent across most subgroups. The number of completed chemotherapy cycles was similar in both treatment groups.
The survival benefit for patients treated with GEMCAP compared with GEM corresponds to the positive effect in the ESPAC-4 trial (median OS 28.0 vs. 25.5 months; HR=0.82, 95% CI 0.68-0.98, p=0.032).[10] Our study thereby confirms the findings of the ESPAC-4 trial in an unselected nationwide cohort. The superiority of

GEMCAP on OS in our study appears to be even greater when compared with the ESPAC-4 study. However, differences in patient characteristics may explain the large difference to some extent. Both the present study and the ESPAC-4 trial excluded patients treated with neoadjuvant therapy and patients who underwent R2 resections. The ESPAC-4 trial also excluded patients with a poor performance status (WHO ≥2), while the present study included 7% of patients with WHO ≥2.[10] Several baseline characteristics in the ESPAC-4 trial were worse than in this nationwide cohort; for example, co-morbidity, R1 resection rate, and nodal disease. Nonetheless, these differences existed in both treatment groups, thus this cannot explain the larger treatment effect of GEMCAP found in the current study. A possible explanation for the larger survival benefit of GEMCAP compared with the ESPAC-4 trial is that our patients were not randomized, with subsequent risk of confounding by indication. Although our study showed no difference in baseline characteristics between GEMCAP and GEM and the benefit remained after adjustment for relevant prognostic factors, the possible influence of residual confounding increasing the effect cannot be completely ruled out. Of note, the proportion of patients with pancreatic cancer who are eligible for both surgery and adjuvant therapy is limited. The findings therefore apply to only this subset of patients. However, our patient selection is less restrictive than in clinical trials on adjuvant chemotherapy.

The median OS of patients treated with GEM in our study (22.1 months) and in the ESPAC-4 trial (25.5 months) was lower than the median OS with GEM found in both the PRODIGE 24 trial (35.5 months) and the APACT trial (36.2 months, abstract available only).[11] This might be attributed to the more stringent selection criteria in these randomized studies, including only patients with a good performance status (WHO score 0-1) and with a serum carbohydrate antigen (CA) 19-9 level below 180 U/mL (PRODIGE) or below 100 U/mL (APACT). No criteria on CA 19-9 level was used in either the ESPAC-4 trial and the current study. Another explanation could be a difference in receipt of palliative treatment in case of disease recurrence. This data is unknown for the current study. However, a previous Dutch nationwide study among PDAC patients who underwent resection showed that only 31% of the patients with symptomatic recurrence and 48% of the patients with asymptomatic recurrence received palliative treatment.[31] Due to these inequalities between randomized studies, it is difficult to make a direct comparison between the intervention arms of different randomized studies (e.g., GEMCAP, mFOLFIRINOX, and nab-paclitaxel plus gemcitabine). Randomized trials with direct comparisons are required to assess which of these contemporary multi-agent chemotherapy regimens shows the most favorable results.

We found that treatment with GEMCAP was associated with better OS than GEM alone, for patients with a positive and negative resection margin. This is in contrast with the ESPAC-4 trial, in which the survival benefit of GEMCAP was only

demonstrated in patients with a negative resection margin.[10] Both international and national guidelines do not distinguish between patients with positive and patients with negative resection margins.[20,21] Our study confirms that the choice of therapy should not depend on resection margin status. Furthermore, GEMCAP seems to result in a larger survival benefit compared to GEM in patients with a better performance status compared to patients with a poorer performance status. However, only a limited number of patients with a poor performance status (WHO=2) were included in this study. The interpretation of the impact of performance status on the found survival benefit is therefore hampered.

The addition of capecitabine to gemcitabine does not seem to result in less cycles of gemcitabine. The proportion of patients receiving a minimum of six cycles was similar in the GEMCAP group (69%) compared with the GEM group (62%). Adverse events and dose intensities were not available for our study population, but the ESPAC-4 trial observed no differences in reported adverse events between both treatment groups (26% vs. 25%, $p>0.05$).[10] In addition, a randomized trial comparing GEMCAP to GEM in patients with locally advanced PDAC showed acceptable levels of toxicity for both treatment groups.[14]

The use of GEMCAP increased after the results of the ESPAC-4 trial were published in March 2017.[10] The use of GEM alone also decreased over time due to the introduction of adjuvant mFOLFIRINOX. Overall, the number of patients who received adjuvant chemotherapy declined due to the increased use of neoadjuvant strategies in more recent years. The Dutch nationwide PREOPANC-2 study comparing two neoadjuvant strategies for patients with resectable or borderline resectable PDAC was initiated in June 2018, with neoadjuvant treatment precluding eligibility for the current study.[32]

This is the first study comparing adjuvant GEMCAP with adjuvant GEM in resectable PDAC in daily clinical practice. However, some limitations of this study should be taken into account. First, the number of patients receiving GEMCAP was only 164 patients, resulting in wide confidence intervals. Second, data on recurrence, palliative treatment, quality of life, and adverse events were not available, thereby precluding additional comparisons such as disease-free survival and toxicity. As a result, we cannot conclude what the impact of both adjuvant chemotherapies is on disease-free survival, how palliative treatment might have affected the overall survival, and what the impact of possible side effects has been. Third, inherent to the retrospective study design, some data (e.g., tumor size and WHO performance status) were incomplete, which was addressed by multiple imputation in the multivariable Cox regression analysis. Fourth, although we adjusted for many variables, not all possible prognostic variables (e.g., CA 19-9 and smoking) were available, with subsequent risk of residual confounding.[33] Fifth, our study population differs from the current patient population as mFOLFIRINOX was introduced in 2019, which is currently considered

the preferred adjuvant treatment for most eligible patients.[20,21] Last, patients who received neoadjuvant therapy were excluded from our study, thereby limiting the generalizability to this specific population.

To conclude, this nationwide study demonstrated that the GEMCAP is associated with better OS as compared to gemcitabine monotherapy. The proportion of patients receiving the planned number of six chemotherapy cycles were similar in both treatment groups. Therefore, adjuvant gemcitabine plus capecitabine should be preferred over gemcitabine monotherapy in patients who are not eligible for mFOLFIRINOX.

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Supplementary material

Table S7.1 – Selected morphologies based on International Classification of Diseases for Oncology (ICD-O-3, pages 69-218).

Code	Description
8000	Neoplasm, NOS
8001	Tumor cells
8010	Carcinoma, NOS
8011	Epithelioma
8012	Large cell carcinoma, NOS
8020	Carcinoma, undifferentiated, NOS
8021	Carcinoma, anaplastic, NOS
8022	Pleomorphic carcinoma
8031	Giant cell carcinoma
8032	Spindle cell carcinoma, NOS
8033	Pseudosarcomatous carcinoma
8035	Carcinoma with osteoclast-like giant cells
8046	Non-small cell carcinoma
8070	Squamous cell carcinoma, NOS
8071	Epidermoid, keratinizing
8072	Epidermoid, large cell, nonkeratinizing
8140	Adenocarcinoma, NOS
8141	Scirrhous adenocarcinoma
8143	Superficial spreading adenocarcinoma
8144	Adenocarcinoma, intestinal type
8145	Carcinoma, diffuse type
8154	Mixed pancreatic endocrine and exocrine tumor
8163	Pancreatobiliary neoplasm
8201	Cribriform carcinoma
8211	Tubular adenocarcinoma
8255	Adenocarcinoma with mixed subtypes
8310	Clear cell adenocarcinoma, NOS
8440	Cystadenocarcinoma, NOS
8480	Mucinous adenocarcinoma
8481	Mucin-producing adenocarcinoma
8490	Signet ring cell carcinoma
8500	Ductal carcinoma, NOS
8510	Medullary carcinoma, NOS
8521	Infiltrating ductular carcinoma
8523	Infiltrating duct mixed with other types of carcinoma
8560	Adenosquamous carcinoma
8570	Adenocarcinoma with squamous metaplasia
8572	Adenocarcinoma with spindle cell metaplasia
8575	Metaplastic carcinoma, NOS
8576	Hepatoid adenocarcinoma

PART IV

Discussion, summary, and addenda

CHAPTER 8

General discussion and future perspectives

Discussion

Cancer of the periampullary region is an overarching term of cancer in the pancreatic head, distal bile duct, ampulla of Vater, and duodenum. Periampullary cancer is challenging in regard to diagnostics, perspectives, and treatment. Patients diagnosed with periampullary cancer are often addressed as one group without reporting the outcomes per tumor origin. On the contrary, in randomized controlled trials patients diagnosed with ampullary cancer and duodenal adenocarcinoma are frequently excluded. As a result, evidence about the effectiveness of various treatment options and (inter)national guidelines are missing, as is real-life data to counsel patients. In this thesis, we assessed the treatment modalities and outcomes per periampullary cancer origin, and more specifically in patients diagnosed with ampullary cancer using data from the Netherlands Cancer Registry (NCR).

In this chapter we discuss the main findings of the studies presented in this thesis. We place them in a broader context and address the implications of our findings for clinical practice. In addition, we identify topics for future studies to improve the management and outcome of patients diagnosed with periampullary cancer, especially ampullary cancer.

Data from the Netherlands Cancer Registry

In this thesis, data from the NCR were used to gain insight in the incidence, treatment and outcomes of patients diagnosed with periampullary cancer in the Netherlands. This database contains individual data on patient, tumor and treatment characteristics and information on vital status of all patients diagnosed with a new malignancy since 1989. All data are uniformly collected by trained administrators of the Netherlands Comprehensive Cancer Organisation (IKNL). The completeness of the NCR is estimated to be at least 95%, and the quality of the data is continuously improved and checked.[1] Unfortunately, the NCR does not register, among others, details on the diagnostic process, recurrences and adverse events related to systemic therapy for all periampullary cancers. Nevertheless, population-based cohorts like the NCR provide valuable information on daily clinical practice and the survival outcomes of different treatment options in an unselected patient population.

The incidence of periampullary and ampullary cancer

Periampullary cancer makes up approximately 5% of all gastrointestinal tumors.[2,3] In line with previous studies, we found that also in the Netherlands pancreatic ductal adenocarcinoma is the most frequent periampullary cancer, followed by

distal cholangiocarcinoma, ampullary cancer, and duodenal adenocarcinoma.[4-6] In 2019, 2860 patients were diagnosed with pancreatic cancer (including pancreatic ductal adenocarcinoma), 235 with distal cholangiocarcinoma, 191 with ampullary cancer, and 161 with small bowel cancer (including duodenal adenocarcinoma) in the Netherlands.[7] The number of patients diagnosed with pancreatic ductal adenocarcinoma and duodenal adenocarcinoma has increased the past decades, while the number of patients with distal cholangiocarcinoma remained stable.[8-10] Between 2004 and 2012, Hester et al. studied the periampullary cancer patients using the National Cancer Database of the United States of America (USA) and concluded that the unadjusted incidence rates remained stable between 2004 and 2012.[4] Other national database registries do not report longitudinal incidence per periampullary cancer origin.

In **chapter five** of this thesis, we studied the incidence of ampullary cancer in the Netherlands, which was 0.59 per 100,000 in 1989-1994 and 0.68 per 100,000 in 2010-2016, with an estimated annual percentage of change of +0.63%. In the USA, France, and South Korea an increase was observed as well, but the incidence remained relatively stable in England.[5,11-13] The question arises whether the increased incidence of ampullary cancer is valid, or a result of improved diagnostic modalities over time or the changed perception that periampullary tumors should be addressed as different entities. However, as the increase in incidence was seen in more periampullary cancers, it cannot only be attributed to improved differentiation between the four periampullary cancers. The rise in the number of patients could also be attributed to the aging of the population, which results in more cancer cases worldwide.[14,15] In addition, the lifestyle in Western countries changed, whereby patients are more exposed to risk factors such as obesity, alcohol use, and diabetes mellitus.[8,9,16-18] Yet, over time, more and better diagnostic modalities became available. This was also shown by the decreasing rates of patients with an unknown TNM stage in the NCR. In addition, the international survey study among surgeons and medical oncologists (**chapter six**) showed that they are aware of the importance to distinguish between the four tumor origins. The overall survival differs per tumor origin and the response to systemic therapies has shown to be different between periampullary tumors. As a result of all of the above, ampullary tumors previously might have been registered as pancreatic ductal adenocarcinoma. Furthermore, registration as pancreatic ductal adenocarcinoma is beneficial for patients to participate in clinical trials. In more recent years, however, ampullary tumors are registered as a separate entity.

Differentiation between periampullary tumors

The diagnosis of and differentiation between periampullary cancer is challenging. The four periampullary tumors are characterized by similar cancer-related symptoms and diagnostic findings which complicates the differentiation between the tumor origins. Various imaging modalities to visualize and indicate the anatomic origin of the primary tumor are used. In the preoperative setting a combination of endoscopic ultrasound, endoscopic retrograde cholangio-pancreatography, CT and/or MRI scan are being performed.[19-23] If possible, histology or cytology can be obtained simultaneously with the endoscopic procedures for pathological assessment. Pathological assessment of the resection specimen, obtained by surgical resection, is seen as the gold standard to establish whether the tumor is benign or malignant and what the anatomic tumor origin is. Currently, pathologists determine the origin of the tumor macroscopically based on the location of the tumor bulk accordingly to the classification of the World Health Organization.[24,25] In addition, the histologic subtype (i.e., pancreatobiliary, intestinal, or mixed) is more frequently studied. Our systematic review showed that it is still unclear which (combination of) diagnostic modalities are best to differentiate between benign and malignant ampullary tumors (**chapter four**). The limited number of studies available and included in our review were mainly retrospective studies, the study populations were too small and heterogeneous to perform a meta-analysis, and the studies were of moderate quality. A prospective study is needed to study the most accurate diagnostic modality for patients suspected of an ampullary tumor.

Van Roessel et al. reported that in 22% of the patients with a periampullary tumor, the preoperative diagnosis of the tumor origin had to be corrected after pathological assessment of the resection specimen.[26] The concordance could not be improved when preoperatively cytology or histology was obtained. However, Pomianowska et al. reported that reassessment of the slides of the resection specimen of a periampullary tumor by two other and experienced pathologists led to a reassignment of the tumor origin in 27% of the patients.[27] The more experience a pathologist had, the less reclassifications were needed. This indicates that the pathological work-up should be performed by specialized pathologists.

In our study on periampullary cancer (**chapter two**), the proportion of patients with non-metastatic disease who underwent surgery varied from one third of the patients diagnosed with pancreatic ductal adenocarcinoma to two thirds diagnosed with ampullary cancer. If one would expect that misdiagnoses are more common among patients who did not undergo surgery, the largest proportion misdiagnosed patients is probably found in the group pancreatic

ductal adenocarcinoma. Moreover, it is suggested that physicians choose a default diagnosis of pancreatic cancer when in doubt, because of the higher likelihood.[24] As a result, the overall survival reported in **chapter two** might be overestimated for pancreatic ductal adenocarcinoma, because this group probably included patients with ampullary cancer and/or duodenal adenocarcinoma which are associated with higher survival rates. However, when the majority of these misclassified patients with ampullary cancer and/or duodenal adenocarcinoma did not undergo resection, the overestimation might be limited as patients not suitable for resection are often patients with a worse prognosis. Periampullary cancers (i.e., distal cholangiocarcinoma, ampullary cancer or duodenal adenocarcinoma) are preoperatively more often misdiagnosed as pancreatic ductal adenocarcinoma (21%) than pancreatic ductal adenocarcinoma are misdiagnosed as one of the other periampullary cancers (13%).[26] Subsequently, the survival rates of the non-metastatic periampullary tumors may differ even more per tumor origin than we now have shown in this thesis.

The difficulty in differentiation between periampullary cancer origins raises separate questions for patients with synchronous metastatic disease. For these patients, no pathological assessment of the resection specimen, which is seen as the gold standard for the diagnosis, can be performed. The tumor origin is mainly based on imaging and pathological assessment of a metastatic site. As the outcome of the metastatic disease of the four origins of periampullary cancers are comparable, the differentiation seems to be less important compared with patients with non-metastatic disease. For patients with metastatic ampullary cancer we reported a median overall survival of 5.9 months (95% CI 4.7-7.1) between 2010 and 2016 in **chapter five**, irrespective of the (anti-tumor) therapy they received. Patients with pancreatic ductal adenocarcinoma had a median overall survival of 6 months when treated with chemotherapy and 2 months when receiving best supportive care only (1997-2016).[8] Irrespective of treatment, this was 4 months for patients with distal cholangiocarcinoma (2009-2016), and around 4-5 months for patients diagnosed with duodenal adenocarcinoma (1999-2013).[9,10] On the other hand, the reliability of the homogeneity of these groups and with it the survival rates can be questioned as well. Yet, no studies reported the proportion of misdiagnoses in a metastatic study population. Moreover, the management – and especially the counseling - of the patients is different per tumor origin, as well as study options. While for patients with pancreatic ductal adenocarcinoma and distal cholangiocarcinoma palliative systemic therapy has proven to (minimally) improve the life-expectancy and is reimbursed, these data are lacking for ampullary cancer and duodenal adenocarcinoma. At least up to 2019, similar palliative systemic therapy regimens

were administered to patients with different periampullary cancer origins suggesting that knowing the primary tumor origin has had limited consequences until today (**chapter two**).

However, it is expected that in the near future tumors will not only be differentiated based on the anatomic origin of the bulk of the primary tumor and histological subtype. In addition, the molecular profile of the tumors are expected to result in precision cancer therapies. For example, mutations of the WNT pathway are more frequent in the intestinal subtype, while KRAS and TP53 mutations are more prevalent in the pancreatobiliary subtype.[28] In addition, microsatellite instability has been reported in approximately 18% of the ampullary tumors, predominantly in the intestinal subtype, and in 35-52% of the duodenal adenocarcinoma.[29-32] This is higher than the percentage of microsatellite instability found in colon cancer, i.e. 15%, in which routine microsatellite instability screening is part of the diagnostic work-up.[33] Furthermore, screening on microsatellite instability in patients with metastatic disease (irrespective of tumor origin) will be done more frequently in the near future, because for the patients with mismatch repair deficiency or microsatellite instability and not responding on standard treatment, nivolumab will be reimbursed.[34] Including this screening for ampullary cancer in order to differentiate should therefore be considered.

Surgical management of ampullary cancer

We have demonstrated that over time more ampullary cancer patients underwent a resection: 50% in 1989-1995 vs. 64% in 2010-2016. We expect that the observed survival improvement in patients diagnosed with ampullary cancer seen in recent diagnosis years (from 2003 onwards), which decreased after adjusting for treatment, is mainly caused by the improvement in the surgical management of these patients over the past decades. In the Netherlands, centralization of pancreatic surgery to hospitals where a minimum of 20 pancreatic resections are performed each year, was initiated in 2011 and officially regulated from 2013 onwards. Due to the increased hospital-volume, perioperative patient care improved, in-hospital mortality decreased and overall survival improved of patients who underwent a pancreatoduodenectomy.[35-37] The median overall survival of patients that underwent pancreatoduodenectomy in the Netherlands was 10.2 months in 2009-2011 and 11.2 months in 2015-2017.[38] Furthermore, Van der Geest et al. showed that the survival rates were significantly better among patients who underwent resection in centers which performed 20 or more procedures compared to those who underwent resection in centers which performed less than 20 procedures annually (HR=1.13; 95% CI 1.02-1.24).[37] In 2012, the Enhanced Recovery After Surgery (ERAS) Recommendations were published to improve recovery after pancreatoduodenectomy.[39] This report contains

recommendations regarding, for example, the indications for preoperative biliary drainage and the nutritional status and guidance by a dietician pre- and postoperatively.[40] Besides centralization of surgical care, resection techniques itself improved, i.e. the introduction of minimally invasive strategies and more reliable anastomosis methods.[41,42] In the Netherlands, a surgical training program to introduce laparoscopic pancreatoduodenectomy was introduced in 2014. Another effect of the centralization is that physicians in the expert centers evaluated and treated more ampullary cancer patients. This resulted in an improved patient selection for surgery.

Use of chemotherapy in ampullary cancer

Centralization of pancreatic surgery might also be the cause of the slightly increased use of (neo)adjuvant therapy among patients with ampullary cancer (3% in 1989-1995 to 8% in 2010-2016; **chapter five**). Accordingly, Van der Geest et al. reported that more patients with pancreatic adenocarcinoma receive adjuvant therapy after pancreatoduodenectomy in high-volume centers, i.e. more than 40 resections, compared with low-volume centers.[37] At the same time, with the centralization further improvement of the pancreatic and periampullary cancer care networks occurred.[38] The referral patterns from non-expertise centers to expertise centers improved with the emerging oncology networks. In addition, the multidisciplinary teams at the expertise centers were more frequently consulted by physicians of non-expertise centers where patients often – closer to home – continue their systemic treatment.[38] From 2018 onwards, with the start of the PACAP-1 trial to implement the best practices of pancreatic cancer care, counseling for adjuvant therapy is performed in the Dutch pancreatic expertise centers.[43] The increased proportion of patients diagnosed with periampullary cancers receiving adjuvant therapy in our study is likely the result of these efforts.

The increased use of chemotherapy might also be attributed to the fact that more systemic treatment options (e.g., combination therapies) became available in the past decade.[44-46] **Chapter three** confirmed that patients diagnosed with ampullary cancer are frequently treated according to the guidelines for pancreatic cancer, that is, with adjuvant FOLFIRINOX or gemcitabine-capecitabine. Moreover, the respondents of our international survey study on ampullary cancer in **chapter six** stated that they adhere to the pancreatic cancer guidelines for patients with ampullary cancer. In addition, the majority of the respondents opt for adjuvant chemotherapy for patients with ampullary cancer irrespective of histologic subtype. Yet, the number of patients receiving adjuvant therapy in the Netherlands remains limited when compared with the results of the survey study and of other studies.[4,11,15] In the Netherlands, 8% of the patients with ampullary cancer were treated with (neo)adjuvant therapy (2010-

2016), of which the majority received adjuvant chemotherapy (**chapter five**). A population-based study in the USA reported a significantly higher proportion: 46% received adjuvant chemotherapy in 2010-2012.[4] In a single-center study in Seoul, 46% of the patients with ampullary cancer were treated with adjuvant chemo(radio)therapy (1997-2012).[15] However, these percentages were calculated among ampullary cancer patients who underwent resection, while we studied the percentage among all patients. Therefore, it cannot be compared to the Dutch numbers. Differences in adjuvant chemotherapy use between countries have been reported in more cancer types, e.g., breast cancer and colorectal cancer.[47-49] Due to a variety of reasons, such as culture, interpretation of published research, healthcare policies, and resources, these practice differences between countries are legitimate.

The reluctance of physicians in the Netherlands to use adjuvant chemotherapy for ampullary cancer could be attributed to the unconfirmed benefit of adjuvant chemotherapy regarding overall survival in patients with ampullary cancer. No high level evidence is available, apart from the subgroup analysis among 304 ampullary cancer patients in the ESPAC-3 (v2) trial, which is published as an abstract only and showed a potential survival benefit for adjuvant chemotherapy.[50] Hence, we studied the added value of adjuvant therapy in ampullary cancer in real-life, a second best option. The results of this analysis are reported in **chapter two**. However, we should be careful in interpreting these results as only 691 patients underwent resection and were therefore candidates for adjuvant therapy. Among the 70 patients who did receive adjuvant therapy no statistically significant survival benefit was reported (HR=0.87 (95% CI 0.62-1.22), p=0.423). Even though we have not been able to demonstrate an association between adjuvant therapy and overall survival benefit in patients with ampullary cancer in the studies described in this thesis, the question to what extent adjuvant chemotherapy could play a role in the management of ampullary cancer remains. The studies reported in this thesis were not only performed in small study populations, but also with retrospectively collected data. In addition, we have no information on the number of chemotherapy cycles and the dose intensity patients received. The analyses were thus performed in a heterogeneous study population, hampering the interpretation.

The largest trial that studied adjuvant chemotherapy among patients with ampullary cancer only was the aforementioned ampullary cancer ESPAC-3 (v2) phase trial (published as a Meeting Abstract for the 2011 ASCO Annual Meeting): patients were randomized in one of the three study arms: adjuvant gemcitabine (n=98), adjuvant 5-fluorouracil monotherapy (n=101), or observation (n=105).[50] The reported median overall survival rates of 57 months for adjuvant gemcitabine

or 5-fluorouracil and 43 months for observation (HR=0.85 (95% CI 0.61-1.18), p=0.32) suggest a potential benefit for adjuvant chemotherapy that failed to reach statistical significance, possibly because of the small numbers. The few other randomized controlled trials available presented data for patients with at least one of the other periampullary cancers, but did not report a pre-specified subgroup analyses per periampullary cancer origin.[51,52] Some single-center observational studies did report improved survival rates after adjuvant chemo(radio)therapy, others did not.[53-55] Ecker et al. performed a multinational retrospective study (n=357) among twelve institutions and concluded that adjuvant chemo(radio)therapy did not improve overall survival among patients with ampullary cancer.[56] On the other hand, another meta-analysis, including ten retrospective studies (n=3361), demonstrated a statistically significant advantage with adjuvant chemoradiotherapy (HR=0.75) in patients with ampullary tumors.[57] Bonet et al. suggested in a systematic review that mainly patients diagnosed with ampullary cancer and positive lymph nodes or T3-4 stage disease might benefit from adjuvant chemo(radio)therapy.[58] The mixed results on the efficacy of adjuvant therapy might be explained by the extensive heterogeneity among the patients diagnosed with this rare cancer. Therefore, to assess the efficacy of adjuvant therapy among patients with ampullary cancer, international randomized controlled trials are needed. Chemotherapy regimens which have shown a survival benefit in pancreatic ductal adenocarcinoma and colorectal cancer should be studied (per histologic subtype), but with increasing knowledge on the molecular profile, systemic therapies should eventually also be studied in clinical trials.

Of note, in this thesis we mainly focused on patients diagnosed with non-metastatic disease. At the same time, the poor median survival found for patients diagnosed with metastatic disease highlights the need to further explore treatment options in this setting. Over time, more patients in the Netherlands have been treated with chemotherapy regimens such as CAPOX or FOLFOX despite the lack of evidence of a survival benefit. The ABC-02 trial reported that gemcitabine plus cisplatin was associated with a survival advantage compared with gemcitabine alone in patients with advanced biliary cancer (n=410), including ampullary cancer (n=20).[59] The median overall survival was 11.7 months among the gemcitabine plus cisplatin group and 8.1 months among the patients in the gemcitabine group (HR=0.64 (95% CI 0.52-0.80), p<0.001).[60] In patients with such short life expectancy, the usefulness of these treatment modalities deserves extra attention. The efficacy of a treatment must be weighed against the side effects and a patients' quality of life. By improving prognostic and predictive markers, patients who are legitimately expected to benefit from systemic therapy can be selected more accurately. Hence, patients who are defined as ineligible

or in whom therapy is considered unbeneficial will not be exposed to systemic toxicities.

Subtypes of ampullary cancer

In the current studies, presented in this thesis and published by others, periampullary cancers are differentiated based on the anatomic tumor origin. Yet, in ampullary cancer specimens, pathologists found three different subtypes based on histologic characteristics: intestinal, pancreatobiliary, and mixed subtype.[61] The subtypes can be explained by the confluence of both intestinal (duodenum) and pancreatobiliary structures (common bile duct and pancreatic duct) from which tumors may arise. It is reported that ampullary patients with an intestinal subtype have a better prognosis compared with ampullary patients with a pancreatobiliary or mixed subtype and that the outcome after adjuvant therapy is different.[12,62-64] Differentiating periampullary cancers based on histologic subtype might therefore be necessary. Moekotte et al. reported, based on a propensity matched cohort study, that gemcitabine-based adjuvant chemotherapy might be effective in ampullary cancer with pancreatobiliary or mixed subtype only.[65] This corresponds with a German retrospective study, which showed a survival benefit of adjuvant gemcitabine in the pancreatobiliary subtype.[66] Furthermore, gemcitabine-based chemotherapy has already proven efficacy in pancreatic ductal adenocarcinoma, which is predominantly a pancreatobiliary cancer, but not in intestinal cancers.[67,68] In line with this, adjuvant mitomycin C and 5-fluorouracil did not result in improved overall survival in a prespecified analysis of ampullary patients (n=48) in a multicenter randomized controlled trial among patients with pancreatic, gallbladder, bile duct, or ampullary cancer (i.e. predominantly pancreatobiliary cancers).[69] The respondents of the international survey study (**chapter six**) reported accordingly. The majority of the respondents considered adjuvant FOLFIRINOX, gemcitabine monotherapy or gemcitabine plus cisplatin for patients with the pancreatobiliary and mixed subtype. These chemotherapy regimens are used for patients with pancreatic ductal adenocarcinoma and/or biliary tract cancer. In contrast, for patients with intestinal subtype adjuvant FOLFOX/CAPOX was preferred. While evidence of beneficial effects on survival are still lacking in adjuvant setting, retrospective studies showed that these chemotherapy regimens improve overall survival in advanced small bowel adenocarcinoma and ampullary cancer.[70,71] Moreover, adjuvant FOLFOX/CAPOX is recommended in colon cancer.[72-74] In the absence of data for small intestine cancers, which is in close resemblance to the intestinal subtype of ampullary cancer, the colon cancer treatment has been extrapolated. On the other hand, FOLFOX is also approved as second-line chemotherapy regimen in patients diagnosed with metastatic bile duct cancer, which indicates that it could be beneficial for patients with the pancreatobiliary

subtype as well.[75] The indications that the effect of chemotherapy regimens depends on the histologic subtype of the ampullary cancer are extra explanations for the variety of chemotherapy regimens used as adjuvant and palliative treatment reported in **chapter three**.

Prognosis per periampullary tumor

In the Dutch nationwide study presented in **chapter two** we showed the difference in overall survival between patients diagnosed with periampullary cancer per anatomic origin. The three-year overall survival of patients diagnosed with non-metastatic ampullary cancer was highest (37%), followed by duodenal adenocarcinoma (34%), distal cholangiocarcinoma (21%) and pancreatic ductal adenocarcinoma (11%). These differences in survival rates are in line with previous population-based studies and single-center studies among patients who underwent resection.[4,6] The survival rate was affected by TNM stage and resection rate, but the exact role of adjuvant therapy and other biological factors remain unknown.

For patients with ampullary cancer, we showed that median overall survival among all patients, irrespective of TNM stage, improved over time in the Netherlands from 14.2 months in 1989-1995 to 18.3 months in 2010-2016 (**chapter five**). As discussed, improvements in care have been found in surgical approaches, as in perioperative care, and the increased use of chemotherapy. The developments are small steps forward. Additional studies on prognostic factors and therapies are desirable. Currently, the International Study Group on Ampullary Cancer are preparing the first phase 3 study to assess the efficacy of adjuvant chemotherapy in patients diagnosed with ampullary cancer. Furthermore, the same research group is intending to reach consensus among pathologists regarding the pathological assessment. To continue improving the survival rates, we should aim to collaborate within this study group and researchers from multiple disciplines.

Chemotherapy in pancreatic ductal adenocarcinoma

As a result of the ESPAC-4 trial, we expected the majority of patients was treated with gemcitabine plus capecitabine as alternative for (modified) FOLFIRINOX.[76] However, we saw that gemcitabine alone is still being administered frequently. Medical oncologists seem to be hesitant to administer gemcitabine plus capecitabine, which could be attributed to the differences observed between positive and negative resection margins in the ESPAC-4 trial.[76] In patients with a positive resection margin, gemcitabine plus capecitabine did not result in a statistically significant improved overall survival when compared with

gemcitabine monotherapy. Furthermore, physicians might be reluctant to administer gemcitabine plus capecitabine out of fear of adverse events and the possibility that the planned number of cycles cannot be administered when compared with a regimen of gemcitabine monotherapy. In the ESPAC-4 trial more grade 3-4 adverse events were reported in the gemcitabine plus capecitabine treatment group (63% vs. 53%). Our study, using real-world data of patients treated with gemcitabine plus capecitabine versus gemcitabine monotherapy showed that comparable rates of completion of adjuvant chemotherapy were reached in both treatment groups (70% vs. 63%; p=0.11).[76]

The Dutch Committee on Assessment of Oncological Medicaments (Commissie BOM) first judged the clinical value of gemcitabine plus capecitabine in 2017 by consulting the PASKWIL-criteria.[77] However, the PASKWIL-criteria require an assessment of the absolute 3-year overall survival benefit (>5% or >3% and HR<0.7), which were not available in the ESPAC-4 trial due to limited median follow-up time (<3 years).[76] The committee therefore concluded that no advice could be given and that the long-term results of the ESPAC-4 trial should be awaited. The long-term results, with a median follow-up time of 60 months, were published in 2020 as abstract at the ASCO Annual Meeting, which demonstrated an increase of 5% (HR=0.84 (95% CI 0.70-0.99), p=0.049) in 5-year overall survival with the addition of capecitabine to adjuvant gemcitabine.[44] Hence, the PASKWIL-criteria are fulfilled and the Dutch guideline included the advice to administer adjuvant gemcitabine plus capecitabine if FOLFIRINOX is contraindicated.[23] Only in 2022, the Dutch 'Commissie BOM' officially published a positive advice, but also noted that a direct comparison between gemcitabine plus capecitabine versus FOLFIRINOX has not been studied.[78] The ESMO Magnitude of Clinical Benefit Scale (≥3% but ≤5% improvement at ≥3 years follow-up) confirmed that the long-term results of the ESPAC-4 trial present a high level of clinical benefit for gemcitabine plus capecitabine when compared with gemcitabine monotherapy.[79]

The treatment of patients diagnosed with pancreatic ductal adenocarcinoma is a rapid evolving field due to efforts made by pancreatic centers worldwide. In the Netherlands, the PREOPANC studies are of great interest. Until recently, resection followed by adjuvant chemotherapy was the cornerstone of the treatment of patients diagnosed with (borderline) resectable disease. However, due to the findings of trials such as the PREOPANC-1 trial, neoadjuvant therapy is emerging.[80-82] In 2020, Cloyd et al. analyzed six randomized controlled trials in which the efficacy of neoadjuvant therapy versus upfront surgery were studied.[82] This meta-analysis concluded that neoadjuvant chemotherapy significantly improved overall survival in resectable and borderline resectable pancreatic

ductal adenocarcinoma. The PREOPANC-1 trial, comparing neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine with adjuvant gemcitabine only, showed a 5-year overall survival rate of 21% with neoadjuvant gemcitabine-based chemoradiotherapy and 7% with upfront surgery.[81] In subgroup analyses, the survival benefit of neoadjuvant chemoradiotherapy was statistically significant in patients with borderline resectable disease (HR=0.62 (95% CI 0.40-0.95), p=0.029), but not in patients with resectable disease (HR=0.96 (95% CI 0.64-1.44), p=0.83).[80] Neoadjuvant therapy will therefore be introduced as the standard treatment approach in the revised Dutch pancreatic cancer guideline (to be published) for patients diagnosed with borderline resectable disease. Currently, results of the PREOPANC-2 trial on neoadjuvant mFOLFIRINOX vs. neoadjuvant chemorardiotherapy are awaited and the PREOPANC-3 trial, in which perioperative mFOLFIRINOX vs. adjuvant mFOLFIRINOX is studied, is recruiting participants with resectable pancreatic ductal adenocarcinoma (NCT-number: NCT04927780).[83] Due to the current developments, it is important to realize that the real-world data presented in **chapter seven** represent a daily clinical practice in which neoadjuvant chemo(radio)therapy was only executed as part of the PREOPANC-1 trial. On the other hand, we should also realize that – as is with every new introduced therapy – not all patients might be fit enough for or willing to undergo (neo)adjuvant chemotherapy. Our findings will therefore still be relevant in daily clinical practice.

Future perspectives

This thesis reports current treatment strategies of patients diagnosed with periampullary cancer, and how worldwide experts manage patients diagnosed with ampullary cancer. The findings of our research confirm the importance of differentiating between periampullary cancer anatomic origins and subtypes, but also adds to the uncertainty on the efficacy of neoadjuvant and adjuvant therapy in patients diagnosed with ampullary cancer. Therefore, future studies should focus on the following main aspects: diagnostic strategies for clear and uniform classification of periampullary cancers, the efficacy of (neo)adjuvant therapy, and molecular profiling searching for drugable targets.

In the reported studies, the periampullary tumors were distinguished based on the anatomic origin of the primary tumor (ICD-O-3). This was performed based on pathological assessments and, if reports were unavailable, on clinical findings. Using the anatomical location to further differentiate is a classic way to name the organ where the tumor originates from: intestinal vs. pancreatobiliary. The relevance to differentiate based on histologic subtype has been highlighted in recent literature.[12,62-64] Patients with the intestinal subtype have better survival rates compared with patients with the pancreatobiliary/mixed subtype. In

addition, the efficacy of chemotherapy seems to be affected by the subtype. Yet, in our population-based studies including ampullary cancer patients, the proportion of patients of which the histologic subtype (i.e., intestinal, pancreatobiliary, or mixed type) was known, was small (23% on average). This might be attributed to the fact that the requirements that must be met to group a tumor as intestinal, pancreatobiliary, or mixed subtype are not uniformly stated in guidelines. The criteria first suggested by Kimura et al. and later revised by Albores-Saavedra et al. have been used to classify the histologic subtype in research, but it is unknown whether and to what extent these are used in clinical practice.[61,62,84] First, pathologists should meet consensus on the criteria to define the subtype. Second, to ascertain that all pathologists then use these criteria, the criteria might be included in the manual for TNM-staging. Finally, in order to study the relevance of the histologic subtype, the subtype should be registered in PALGA and included in the NCR and international registries.

Although we could not demonstrate a survival benefit of adjuvant therapy among patients diagnosed with ampullary cancer, it cannot be excluded that there is an association after all. Therefore, new studies, preferably randomized controlled trials, should be initiated. These studies should include a larger study population, but also try to study the association per histologic subgroup and per adjuvant therapy regimen. Following the developments in the management of patients diagnosed with pancreatic ductal adenocarcinoma, attention will also need to go out to neoadjuvant therapy. In the survey study, the respondents did not seem to extrapolate these developments to ampullary cancer yet. Only 24% would apply neoadjuvant therapy. However, with the introduction of neoadjuvant therapy in pancreatic ductal adenocarcinoma, a biopsy will be required prior to start of neoadjuvant treatment to confirm the diagnosis of pancreatic ductal adenocarcinoma. To recruit enough patients to reach adequate statistical power in these studies, international collaboration is essential. With the number of ampullary cancer patients diagnosed in the Netherlands (n=177 in 2021) this statistical power will clearly not be reached within an acceptable time period if only studied in the Netherlands.[7] Worldwide, approximately 9,600 cases are expected annually (0.2% of 4,800,000 gastro-intestinal tumors diagnosed worldwide).[85] To reach enough statistical power and ensure generalizability of the study results, more international multicenter randomized controlled trials are needed. How successful collaboration can be, has been proven by the Dutch Pancreatic Cancer Group (DPCG). Since its establishment in 2011, the DPCG has prosperously completed several multicenter randomized controlled trials and nationwide data registries.[86] This emphasizes the potential of the International Study Group on Ampullary Cancer. Moreover, an international real-world data registry for patients diagnosed with ampullary

cancer is considered valuable according to the respondents of our survey study. The data registry will facilitate and accelerate observations and studies on developments in daily clinical practice.

The Dutch Pancreatic Cancer group also collaborates with the IKNL, which already resulted in an increase of available variables for pancreatic cancer patients in the NCR. The data registered by the NCR is continuously extending, for example by the linkage of the NCR with PACAP PROMs questionnaires which contains information on the quality of life pre-, during-, and post-treatment. In addition, the pathology data registered in PALGA can be connected with the NCR. Improvement in the pathology assessment of ampullary cancer tissue will therefore be noticed by researchers using NCR data immediately. This collaboration should be encouraged and extended for periampullary cancers in order to increase the variables registered in the NCR.

Apart from (neo)adjuvant therapies, molecular profiling is a major topic in cancer research with a great impact on treatment strategies. Targeted therapies are directed against specific molecules in or on cancer cells, as opposed to chemotherapy which is a killer of fast growing and dividing cells (not specifically cancer cells). As we currently see in other types of cancer, more and more targeted therapies are being approved for the treatment of especially advanced and/or metastatic disease.[46,87] With the increased knowledge on and availability of targeted therapy, routine molecular profiling of selected tumors is expected to be standard practice in the near future. Molecular diagnostics, such as whole genome sequencing – for which biopsies and blood samples are needed – gives information on both germline and somatic mutations. These mutations are helpful in the diagnostic process, but can also be targeted with molecular therapy and/or used to predict sensitivity to therapies. In addition, as an alternative when biopsies are difficult to obtain, the circulating tumor DNA can also give information on the tumor genetics. Previous studies have shown germline and somatic alterations in – among others – BRCA2, ERBB2 and ELF3 genes in ampullary cancer. Patients with a BRCA-mutation might be treated with PARP inhibitors.[88-91] Furthermore, deficiencies in mismatch repair, as seen in 14-22% of ampullary cancer, will enable confirmation of diagnosis, predict chemotherapy effect, and might benefit from programmed death-ligand (PD-L1) inhibition.[88,92-96] This immunotherapy, for example nivolumab in metastatic disease with microsatellite instability or mismatch repair deficiency, has shown promising results in other solid tumors, but further research among patients with ampullary cancer is necessary.[34] In the Netherlands, a phase 1b/2a study is initiated to assess the safety and feasibility of neoadjuvant immunetherapy in mismatch repair deficient resectable duodenal adenocarcinoma.[97] Of note, unspecified patients with

pancreatic ductal adenocarcinoma did not benefit from mono-immunotherapy. New treatment strategies are therefore under investigation to prime periampullary cancers for (dual) immunotherapy, which can be done by therapeutic vaccination or by altering the tumor immune microenvironment with traditional chemotherapy.[98]

In conclusion, we have shown that resection is the cornerstone of the treatment of non-metastatic periampulary cancer. The use and effect of (neo)adjuvant therapy varies per periampullary tumor origin and histological subtype. Future studies should focus on accurate differentiation between the four periampullary cancers and identification of the histologic subtype. The histological characteristics are even more important for ampullary cancers, which are shown to be predominantly pancreatobiliary and intestinal. Previous studies have shown that histologic subtype is a prognostic variable for overall survival, but also for the efficacy of systemic regimens. Especially in ampullary cancer, a definite association between adjuvant therapy and overall survival could not be demonstrated so far. More attempts should be made to draw conclusions on the definitive role of (neo)adjuvant therapy in the management of ampullary cancer. With the increased use of targeted therapies in other cancers, molecular profiling should get a more prominent place in the diagnostic work-up of patients with (metastatic) ampullary cancer. To reach advancements in (peri)ampullary cancer care, international collaboration is a prerequisite in order to reach sufficient patient inclusion in future studies investigating patients with (peri)ampullary cancer.

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CHAPTER 9

Summary

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.

ADDENDUM

Nederlandse samenvatting

Nederlandse samenvatting

Periampullaire tumoren is een verzamelnaam van vier verschillende kwaadaardige tumoren die ontstaan vanuit en rondom de papil van Vater. De papil van Vater is de locatie waar de galweg en de afvoerbuis van de alvleesklier uitmonden in de twaalfvingerige darm. Van alle tumoren die gediagnostiseerd worden in het spijsverteringskanaal, zijn ongeveer 5% periampullaire tumoren. Jaarlijks krijgen ongeveer 900 patiënten in Nederland deze diagnose. Hiervan komt kanker in de kop van de alvleesklier het vaakst voor, gevolgd door kanker in het uiteinde van de galweg, in de twaalfvingerige darm en – het minst voorkomend – kanker in de papil van Vater. Patiënten hebben verscheidene symptomen, waaronder een gele verkleuring van de huid, buikpijn en gewichtsverlies.

Voor een zo groot mogelijke kans op genezing is het noodzakelijk om deze tumoren middels chirurgie te verwijderen. In Nederland wordt deze specifieke chirurgische ingreep alleen gedaan in de 15 alvleesklierkanker expertisecentra. Of de patiënten voorafgaand aan de chirurgische ingreep (neoadjuvant) of na deze ingreep (adjuvant) nog behandeld dienen te worden met chemotherapie en/of bestraling is afhankelijk van de precieze locatie van de tumor en van de uitgebreidheid van de tumor. De huidige Nederlandse richtlijn voor de behandeling van alvleesklierkanker adviseert adjuvante chemotherapie. In de herziene versie, welke naar verwachting in 2023 wordt gepubliceerd, zal ook een neoadjuvante behandeling voor een selecte patiëntenpopulatie worden geadviseerd, namelijk aan patiënten waarbij de tumor contact maakt met de bloedvaten. De richtlijn voor de behandeling van galwegtumoren adviseert geen neoadjuvante of adjuvante behandeling te geven op basis van reeds eerder uitgevoerde onderzoeken. Aangezien het zeldzame tumoren betreft, ontbreekt het voor tumoren in de twaalfvingerige darm en de papil van Vater aan voldoende bewijs dat neoadjvante en adjuvante behandelingen zinvol zijn. Daarnaast zijn er ook geen (inter)nationale richtlijnen over de behandelopties van deze tumoren beschikbaar. Om voorlichting van patiënten met periampullaire tumoren te verbeteren, onderzochten wij in dit proefschrift de patiëntkarakteristieken, behandelingen en overlevingscijfers van patiënten met een periampullaire tumor en specifiek die van patiënten met een tumor in de papil van Vater.

Periampullaire tumoren

In dit proefschrift werd eerst de behandeling en overleving van patiënten met een periampullaire tumor in kaart gebracht. Tussen 2012 en 2018 werden in Nederland ruim 8700 patiënten gediagnosticeerd met een periampullaire tumor,

welke bij diagnose (nog) niet uitgezaaid was. De ruime meerderheid van de patiënten had een tumor in de kop van de alvleesklier (68%), gevolgd door een tumor in het uiteinde van de galweg (13%), een tumor in de papil van Vater (12%) en een tumor in de twaalfvingerige darm (7%). Terwijl 70% van de patiënten met een papil van Vater tumor chirurgie ondergingen, ontving maar een klein percentage (11%) neoadjuvante en/of adjuvante therapie. Ook patiënten gediagnosticeerd met een tumor in het uiteinde van de galweg of de twaalfvingerige darm werden beperkt behandeld met neoadjuvante en/of adjuvante therapie. Slechts 35% van de patiënten met een tumor in de kop van de alvleesklier werden chirurgisch behandeld. Echter, een aanzienlijk deel (58%) van deze patiënten met een tumor in de kop van de alvleesklier ontving wel neoadjuvante en/of adjuvante therapie. Deze bevindingen zijn in lijn met de huidige adviezen in de richtlijnen. Ons onderzoek liet tevens zien dat de overleving verschilt per tumor locatie. Patiënten met een tumor in de papil van Vater of twaalfvingerige darm hebben betere overlevingskansen dan patiënten met een tumor in de kop van de alvleesklier of het uiteinde van de galweg. Daarbij zagen wij in ons onderzoek dat het krijgen van adjuvante behandeling wel leidt tot een langere overleving voor de patiënten met een tumor in de kop van de alvleesklier of het uiteinde van de galweg, maar dat dit niet geldt voor patiënten met een tumor in de papil van Vater of twaalfvingerige darm.

Welk type chemotherapie werd voorgeschreven bij de verschillende soorten periampullaire tumoren werd onderzocht aan de hand van data van patiënten met een diagnose tussen 2015 en 2019. Deze data lieten zien dat voor patiënten met een tumor in de kop van de alvleesklier of in het uiteinde van de galweg de richtlijnen geldig ten tijde van diagnose werden gevolgd. Bij patiënten met een tumor in de twaalfvingerige darm lijken de artsen voornamelijk de richtlijn voor dikke darmkanker te raadplegen. Patiënten met een tumor in de papil van Vater werden na de operatie met uiteenlopende typen chemotherapie behandeld. Dit laat zien dat eenduidig bewijs voor de behandeling van patiënten met een tumor in de papil van Vater ontbreekt en dat als gevolg daarvan artsen momenteel meerdere richtlijnen en studies raadplegen.

Papil van Vater tumoren

In het tweede deel van dit proefschrift vestigden we de aandacht op tumoren in de papil van Vater. In een systematisch review gaven we een overzicht van alle gepubliceerde studies die onderzochten in hoeverre een diagnostisch onderzoek (beeldvorming en/of biopten) een goedaardige tumor kan onderscheiden van een kwaadaardige tumor. In totaal werden 10 artikelen geïdentificeerd, welke rapporteerden over in totaal 10 verschillende diagnostische middelen (o.a. CT-scan, PET/CT-scan, endoscopische echografie en biopten). Momenteel wordt in

de dagelijkse praktijk een grote variatie aan diagnostiek ingezet. De endoscopische echografie, waarbij een flexibele slang via de mond door de slokdarm, maag en papil van Vater wordt ingebracht, lijkt het beste te kunnen differentiëren tussen een goedaardige en kwaadaardige tumor van de papil van Vater. Echter, het aantal studies dat deze en andere diagnostische onderzoeken hebben onderzocht, zijn zeer beperkt. Tevens was het aantal geïncludeerde patiënten klein. Aanvullend onderzoek naar de nauwkeurigheid van een (combinatie van) diagnostische onderzoek(en) om de diagnose goedaardige danwel kwaadaardige tumor in de papil van Vater te kunnen stellen, is daarom noodzakelijk.

Vervolgens beschrijven we de patiënten die in Nederland zijn gediagnosticeerd met kanker van de papil van Vater. In totaal werden 3840 patiënten gediagnosticeerd tussen 1989 en 2016, waarvan 9 op de 10 patiënten geen uitzaaiingen hadden op moment van diagnose. Over de tijd ondergingen meer patiënten een operatie: van 50% van de patiënten zonder uitzaaiingen gediagnosticeerd in 1989-1995 naar 64% in 2010-2016. Het aantal patiënten dat werd behandeld met neoadjuvante en/of adjuvante therapie was laag, maar was wel verdubbeld in 2010-2016 ten opzichte van 1989-1995 (8% vs. 3%). Tegelijkertijd werd gezien dat het aantal patiënten dat na 5 jaar nog in leven was, was toegenomen van 1 op de 5 patiënten in 1989-1995 tot 1 op de 4 patiënten in 2010-2016. Deze verbeterde overlevingscijfers zijn mogelijk te verklaren doordat meer patiënten een operatie konden ondergaan, ongeacht of zij aanvullend werden behandeld met chemotherapie en/of bestraling. Echter, de afgelopen jaren zijn ook de chirurgische technieken en zorg rondom de operatie verbeterd en zijn in Nederland de chirurgische behandelingen gecentraliseerd in 15 expertisecentra. Eerder onderzoek heeft aangetoond dat deze factoren bijdragen aan een verbetering in de overleving. Aan patiënten met uitzaaiingen werd over de tijd wel vaker chemotherapie voorgeschreven, maar de overleving verbeterde hier niet significant door.

Bij gebrek aan een richtlijn voor patiënten met een tumor in de papil van Vater kan worden verwacht dat er een grote variatie wordt gezien in hoe artsen deze patiënten behandelen. We hebben middels een internationale vragenlijst onderzocht hoe momenteel deze patiënten worden gediagnosticeerd en behandeld. Van de 217 chirurgen en medisch oncologen die onze vragenlijst hebben ingevuld, werkten 9 op de 10 in een expertisecentrum voor alvleesklierkanker. Zij gaven aan dat zij voornamelijk de fitheid van de patiënt, de aan- of afwezigheid van uitzaaiingen, de aan- of afwezigheid van tumorcellen in de lymfeklieren, de grootte van de tumor en in hoeverre de tumor volledig is verwijderd door de chirurg, meenemen in de behandelkeuze. Terwijl 1 op de 4

specialisten aangaf dat zij neoadjuvante therapie zouden overwegen, werd adjuvante therapie overwogen door 9 op de 10 specialisten. De chemotherapie die de specialisten vervolgens kiezen, zijn voornamelijk therapieën die ook voorgeschreven worden aan patiënten met alvleesklierkanker, galwegkanker of dikke darmkanker. De chirurgen en oncologen benoemden dat er in de afgelopen 5 jaar positieve ontwikkelingen in de zorg hebben plaatsgevonden, waaronder de beschikbaarheid van meerdere chemotherapieën, verbeteringen in operatietechnieken, en de toegenomen kennis over de eigenschappen van de tumor en hoe deze het effect van een behandeling beïnvloeden. Echter, deze studie bevestigde nogmaals dat een richtlijn gewenst is. Een internationaal register van patiënten met een tumor in de papil van Vater en klinische studies naar de effectiviteit van chemotherapie en doelgerichte therapieën zullen nodig zijn om patiënten de beste behandeling – gebaseerd op kwalitatief goede studies – te geven en uiteindelijk de prognose van deze patiënten te verbeteren.

Alvleesklierkanker

Tot slot hebben we in dit proefschrift bekeken welke adjuvante chemotherapie de beste uitkomst geeft bij patiënten met alvleesklierkanker die niet in aanmerking komen voor FOLFIRINOX (de chemotherapie van de eerste keus). Voor deze patiënten zijn zowel de combinatie gemcitabine plus capecitabine als gemcitabine alleen beschikbaar. Wij zagen dat de kans op overlijden 30% kleiner is voor patiënten die behandeld werden met gemcitabine in combinatie met capecitabine in plaats van gemcitabine alleen. Daarnaast zagen we dat in beide behandelgroepen ongeveer twee derde van de patiënten de chemotherapie van zes kuren volbracht. Dit resulteerde in het advies om patiënten, die een operatieve verwijdering van alvleesklierkanker hebben ondergaan en niet in aanmerking komen voor FOLFIRINOX chemotherapie, bij voorkeur te behandelen met de combinatie gemcitabine plus capecitabine.

ADDENDUM

Impact paragraph

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.

ADDENDUM

List of publications

List of publications

de Jong EJM, Lemmers DHL, Benedetti Cacciaguerra A, Bouwense SAW, Geurts SME, Tjan-Heijnen VCG, Valkenburg-van Iersel LBJ, Wilmink JW, Besselink MG, Abu Hilal M, de Vos-Geelen J. *Oncologic management of ampullary cancer: International survey among surgical and medical oncologists.* Surg Oncol. 2022 Sep 1;44:101841. Online ahead of print.

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*shared first author

ADDENDUM

Dankwoord

Dankwoord

Het dankwoord. Het hoofdstuk dat door velen als eerste, en misschien ook wel als enige, wordt gelezen. Door mij werd het echter, symbolisch, als laatste geschreven. Voor mij illustreert dit hoofdstuk hoeveel deskundige, bijzondere en lieve mensen mij hebben ondersteund gedurende mijn tijd als promovendus. Eenieder heeft op zijn/haar manier bijgedragen aan mijn ontwikkeling als onderzoeker, als arts en als persoon.

Beste **dr. de Vos-Geelen**, lieve Judith. In 2016 heb ik, redelijk willekeurig, jou een mail gestuurd. Of ik niet mijn WIP-stage en/of review onder jouw begeleiding kon doen? Nooit gedacht dat we 7 jaar later samen mijn promotie zouden vieren. Als ik denk aan onze samenwerking de afgelopen jaren, kan ik dat alleen maar doen met een grote glimlach op mijn gezicht. Altijd bereikbaar, altijd enthousiast, altijd motiverend, en vliegensvlug, kritisch en direct in je feedback. Maar vooral, en dat deed mij altijd goed, oprecht geïnteresseerd en uitgesproken trots. Daarnaast ben je ook nog koningin in organisatie en geheugen. Ik ben onder de indruk hoe jij het werk als oncoloog, onderzoeker, co-promotor, begeleider van nog heel veel meer studenten en onderzoekers, partner, moeder en vriendin weet te combineren. Hoewel de frequente overleggen verleden tijd zijn, hoop ik van harte dat we de samenwerking kunnen voortzetten. Mijn interesse in en behoefte naar oncologisch onderzoek doen is alleen maar toegenomen en bij jou is er nooit een gebrek aan ideeën. Tot slot hoop ik de komende jaren je vaker fysiek dan online te zien, je af en toe ook om (professioneel) advies te mogen vragen en zowel in het onderzoek als in de kliniek veel van je te mogen leren. Dankjewel voor deze mooie reis samen.

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In 2023 heb ik mogen starten als AIOS Interne Geneeskunde in Zuyderland Medisch Centrum. Door de opleider **dr. Tummers**, de **stafleden** van de valgroep en de **arts-assistenten** ben ik warm onthaald en de patiënten hebben mij nu al een grote verscheidenheid aan ziektebeelden laten zien. Alles maakt dat ik nóg meer zin heb in de komende opleidingsjaren in Sittard en Heerlen.

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spannender vind dan de discussie van dit proefschrift. Ik kan een hoofdstuk vullen met onze avonturen, maar ik heb toch wel enige zelfcensuur uitgeoefend. Niet alles hoeft openbaar te worden natuurlijk ;-). De supervisor van mijn bachelor onderzoek vertelde mij dat ze nog een studente had gehad die ook de AKO ging starten in 2015: een mooie ingang om jou aan te spreken op de introductiedag van de AKO. Nooit gedacht dat die dag zou leiden tot vele bieb-momentjes, spinningsessies, kookavondjes, werkfeestjes, en zelfs een vakantie. Het thuiswerken was met jou, en onze vrienden van Q-music, een welkome afwisseling met de werkuren alleen in ons corona-proof thuiskantoor. Hoewel anderen misschien denken dat wij niets gedaan kregen (want: wij + thee = veel kletsen), hebben we allebei toch mooi ons proefschrift binnen de beoogde tijd af weten te krijgen. Daarbij zijn er zeker meerdere zinnen in dit proefschrift te danken aan jouw input. Een co-auteurschap had je dus wel verdiend. Dat wij gelijktijdig een promotietraject zijn aangegaan, maakte het uitwisselen van ervaringen en inwinnen van tips en tricks alleen maar makkelijker. Ik vind het enorm bijzonder dat ik deze mooie tijd met jou naast mij mag afronden. Onze toekomst in Pisa als post-docs op endocriene tumoren moeten we misschien nog maar even uitstellen: laten we nu maar eens zien dat we ook het A-gedeelte van de AKO hebben verdiend. Ik voel mij bevoorrecht jou als vriendin te hebben en samen de afgelopen 7,5 (!) jaar te hebben gedeeld. Lieve Pomme, op naar nog vele jaren vol thee, kookavondjes, feestjes, wandelingen, en vakanties.

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Lieve buurvrouw, fietsmaatje, corona-bubbel-huisgenoot, eetmaatje en natuurlijk karaoke-vriendin. Kortom, lieve **Merel**. Je hebt geen medische opleiding gedaan, maar inmiddels kan je een aardig woordje meepraten. Altijd oprecht geïnteresseerd en de voortgang van mijn promotie had je haarscherp in je geheugen. Beiden een volle agenda, maar met grote regelmaat zien en spreken we elkaar. Of het nu op de fiets is, tijdens een wandeling, op de bank, met of zonder eten en in- of exclusief een muziekje: gezellig weten we het altijd te maken. Ik heb wel eens gehoord dat anderen vinden dat we te veel energie hebben… Ik noem ons liever 'ochtendmens', 'overdagmens' of 'avondmens', net wat ons uitkomt. En saai is het in ieder geval nooit.

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Lieve **Janine**, **Lina**, **Astrid** en **Esmee**. Met regelmaat wilde ik de tijd als AKO-student pauzeren: ik had het zo naar mijn zin. Jullie hebben de AKO, die bij wijlen toch erg pittig was met #reflecterenkunjeleren, gemaakt tot een periode waar ik met een grote glimlach aan terugdenk. Van vele uurtjes in de bieb tot lekkere (VGT-)etentjes, en van samen carnavallen tot brownies bakken om te vieren dat we weer een jaar hadden afgesloten. Bedankt meiden. Op naar een mooie toekomst!

Lieve **Vera**, hoewel je voor mijn idee vaker in het buitenland zat (en soms nog zit), heb ik genoeg vrolijke herinneringen samen. Hoewel, bij mij slapen na ons Terug naar Toen feestje staat misschien niet in jouw rijtje. Snel een fietstochtje doen met bestemming terras?! En speciaal voor **Martijn**: DOOD! AF! en AJETOO!

Dreamteam, lieve **Maud** en **Lotte**! Mooie jaren in Maastricht gehad en nu alle drie druk in onze eigen stad met onze studie en carrière. Gelukkig weten we elkaar altijd te vinden en op de hoogte te brengen. Zetten jullie de thee vast klaar voor de volgende date? Neem ik de chocolade mee. De gesprekken volgen vanzelf.

Liefste **Judith**! Vijftien jaar! Vijftien jaar geleden dat we bedachten dat samen op de pont en samen fietsen gezelliger was dan alleen. En dus inmiddels vijftien jaar beste vriendjes. Waar ik heel duidelijk een doel voor ogen had, was jij meer zoekende. Hoe jij daarin altijd je gevoel hebt gevolgd, hoe lastig dat soms ook voor je was, vind ik bewonderenswaardig. En kijk eens wat die zoektocht jou allemaal heeft gebracht! Jij laat mij zien dat tijd ons veel duidelijk kan maken. Echter, we weten allebei ook dat we tijd te weinig hebben: een date plannen blijkt toch best lastig en als we elkaar eenmaal weer zien, hebben we tijd te kort. Ach, dat laatste is alleen maar een goed teken. Lieve Judith, zullen we er nog minstens 15 jaar aan vast plakken?

Jasmijn, weet je nog klas 4C op Het 4e? De klas waar we eigenlijk allebei niet in wilden zitten? Achteraf maar goed dat wisselen van klas niet mogelijk was, want anders hadden we al die leuke momenten niet met elkaar gehad: bijzondere wiskundelessen van Annet, een fantastische Rome-reis, een bijzonder profielwerkstuk met aardappelen en rode pastasaus, een spannende film op de Velvet Ramparts en een hele mooie vakantie naar Sofia. Jij bewijst dat goede vriendschap niet is gebaseerd op hoe vaak je elkaar ziet, maar op hoe goed het voelt als je elkaar weer ziet. En dat laatste, dat voelt meer dan goed.

Mede zij-instromer, lieve **Femke**. Die minor geneeskunde was kneiterhard werken, maar beiden hebben we daarna toch mooi in een verkort traject onze droom kunnen laten uitkomen. Alle mijlpalen weten we gelukkig (soms met enige vertraging) te vieren mét een taartje. Dus, snel weer een taartje eten denk ik zo!

Lieve **Romy** en **Jan-Jacob**. Opeens aan tafel bij familie de Jong en dan ook nog eens een kletsgrage Evelien. Bedankt voor jullie interesse in die wonderlijke wereld waarin ik werk en in het meedoen met die gekke familiefeestjes die ik altijd weer verzin (pannenkoeken, Foute Party)!

Het woord oppasmoeder, lieve **Linda**, dekt niet wat jij voor mij bent en betekent. Goede herinneringen aan onze Shrek Super Party Party's, Scrooge de Dagobert Duck versie en alle keren Pietje Bell. O, en de gehaktballen niet te vergeten. Altijd bij ons thuis, maar samen met **Mat** waren en zijn jullie een veilige haven waar we nog altijd terecht kunnen. Dat ik hier sta is dus ook zeker aan jullie te danken. En je weet het hè Lin, in de toekomst zoeken we een Linda 2.0 voor mijn kinderen.

Lieve **Rick**. Dankjewel dat jij degene bent die zoveel momenten zoveel leuker maakt. Bedankt voor je luisterend oor, het laten weten hoe trots je bent, je zorgzaamheid en vooral voor alle leuke en ontspannen momenten samen. Jij waakt ervoor dat ik mijn vrije dagen als vrije dagen invul. Ik kijk uit naar de mooie avonturen die we in de toekomst samen gaan delen. Is het niet fantastico, dan is het wel stelviotastisch.

Suzanne, liefste Suus! Zussen en beste vrienden. Beter kan niet. Hoewel we enerzijds in veel hetzelfde zijn, kunnen we anderzijds genoeg verschillen benoemen. Zo is het creatieve talent bij jou terecht gekomen. Ik ben dan ook heel blij dat jij de cover hebt ontworpen. Wordt zo'n boekje vol ingewikkeldheid toch een stukje aantrekkelijker van. Hoe jij de afgelopen jaren steeds meer je eigen hart hebt gevolgd en dappere keuzes hebt gemaakt op professioneel en persoonlijk vlak is iets waar ik alleen maar van kan en wil leren. Je bent daarnaast onwijs zorgzaam, altijd bereikbaar om te sparren en adviseren, en vooral altijd in

voor iets leuks: vakanties, festivals en logeerpartijtjes. Wanneer weer een #feestmetSuus? Dikke lebber!

Liefste broer, lieve **Martijn**. Ik zal maar met de deur in huis vallen: jij krijgt een stukje van mijn dr. titel hoor! Hoewel het niet over nefronen gaat, meer dan verdiend. Want wat je zei: alle support verdient wel een beloning. Ik waardeer enorm de interesse die jij altijd hebt getoond in mijn studie en werk. Daarnaast ben ik je dankbaar voor alle mooie, sportieve, en hilarische momenten die we hebben gedeeld. Ik ben onwijs trots op hoe jij – zowel op werkgebied als bij vrienden en familie – voor iedereen klaar staat, hoe leergierig je bent en nog meer op hoe sociaal jij bent. Dat maakt dat die paranimfen-rol je op het lijf geschreven is. Martijn, wanneer halen we weer de tweewielers tevoorschijn? Kies jij maar welke het wordt! Plezier gaan we sowieso hebben.

Lieve **papa** en **mama**. Het is jullie onvoorwaardelijke steun die hebben gemaakt dat ik hier sta. Jullie, die ons laten voelen wat onvoorwaardelijke liefde is. Jullie, die jezelf altijd op de tweede plek hebben gezet. Jullie, die ons alle drie de kansen op mooie opleidingen hebben gegeven. Jullie, die altijd in mij bleven geloven, zelfs na de zoveelste afwijzing voor geneeskunde. Jullie, die mij motiveerden, maar soms juist ook afremden met 'goed is goed genoeg'. Jullie, die mij de ruimte gaven om school en studie altijd met sport en muziek te combineren voor de hoognodige ontspanning. Jullie, die alle keren de reis Amsterdam-Maastricht maken alsof het niets is. Jullie, die altijd op de hoogte zijn van mijn overvolle agenda. Jullie, die thuis altijd thuis hebben gelaten, zelfs na al die jaren op mezelf. Jullie zullen zeggen trots op mij te zijn, maar ik ben degene die het trotst is. Trots op jullie, jullie als ouders en op ons als gezin!

ADDENDUM

Curriculum vitae

Curriculum vitae

Evelien de Jong was born on January 19th 1995 in Amsterdam, where she grew up in a close family with her older sister Suzanne and younger brother Martijn. After completing secondary school at Het 4e Gymnasium in Amsterdam, she started the bachelor Health and Life Sciences at Vrije Universiteit Amsterdam in 2012. She graduated with a major in Biomedical Sciences. In 2015 she was accepted to the 4-year master's program Physician-Clinical Investigator (AKO) at Maastricht University.

During her bachelor and master, Evelien developed an interest in oncology and gastroenterology. Therefore, during the short scientific internship in her second year of the master's program, Evelien studied the treatment and overall survival of patients diagnosed with proximal esophageal cancer using data from the Netherlands Cancer Registry under the supervision of dr. Judith de Vos-Geelen and with statistical help from dr. ir. Sandra Geurts. The clinical rotations that followed confirmed her aspiration to work in the fields of oncology and gastroenterology. Therefore, and given the good collaboration and supervision previously, she once again worked with dr. Judith de Vos-Geelen and dr. ir. Sandra Geurts on a research project on ampullary cancer. Simultaneously, she completed her senior clinical rotation at the Department of Gastroenterology under the supervision of drs. Chantal Hoge. After successfully obtaining her medical degree in 2019, Evelien got the opportunity to expand her previous research to a PhD thesis on the treatment and outcomes of (peri)ampullary cancer. In the subsequent two years, she worked full-time on her PhD thesis at the Division of Medical Oncology in Maastricht UMC+ under the supervision of prof. dr. Vivianne Tjan-Heijnen, dr. Judith de Vos-Geelen, and dr. ir. Sandra Geurts.

As of January 2022, Evelien started as a resident (ANIOS) at the Department of Internal Medicine at MUMC+. For six months she combined her PhD with her work as a resident, whereafter she started working full-time as a medical doctor. In January 2023, she started as a resident in training (AIOS) at the Department of Internal Medicine at Zuyderland Medical Center in Sittard and Heerlen.