GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

Academic Year 2016 - 2017

ENDOSCOPIC VS. SURGICAL APPROACH IN PATIENTS WITH AN AMPULLOMA: A QUALITY OF LIFE AND QUALITY OF TREATMENT STUDY

Karen **DE MOL**

Promotor: Prof. dr. Berrevoet

Dissertation presented in the 2nd Master year in the programme of

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Preface

Ampullomas are benign tumours with a low incidence. (1-8) However, with the ageing population, this rare condition could become more frequent. Fortunately, the treatment techniques for *ampullomas* are improving. Especially the endoscopic treatment is becoming more important, due to its less invasive approach. (3, 9-11) So, a comparative study of surgery and endoscopy is needed.
This thesis describes the differences between endoscopy and surgery, with their own pros and cons. Hereby, the focus will be on the quality of life after both procedures. Surveys were conducted to collect data. The obtained patient-, treatment- and follow-up data were assembled in a database and statistically processed.

At the start, the concept of *ampullomas* was unknown to me. The literature has vastly improved my knowledge, although little could be found about quality of life. Due to this, I encountered a lot of obstacles, that needed to be overcome, both while setting up and writing this thesis. I hope that this thesis might provide an interesting and practical summary about treatment possibilities and quality of life in patients with an *ampulloma*.

My gratitude, first and foremost, goes to my promotor, Prof. dr. F. Berrevoet, for his guidance during this past year and a half. Furthermore, I would like to thank my thesis partner Valentien Merlevede for the collaboration. I am also grateful for the help of Prof. dr. L. Ferdinande and Ms. B. Van Coppenolle (for providing data), Ms. C. Tielemans and Ms. S. Van Driessche (for planning and arranging the appointments). The help of Ms. E. Deschepper with statistical analysis and the help of M. Van Daele with proofreading was very much appreciated.
Lastly, I would like to thank my family and friends for their support.

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ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CACI	Charlson Age-adjusted Comorbidity Index
CBD	Common Bile Duct
CCI	Charlson Comorbidity Index
CECT	Contrast Enhanced Computed Tomography
EP	Endoscopic Papillectomy
EPD	Electronic Patient Dossier
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS	Endoscopic Ultrasound
GGT	Gamma-Glutamyl Transpeptidase
HRQL	Health-Related Quality of Life
Intraductal US	Intraductal Ultrasound
MRI	Magnetic Resonance Imaging
N	Number of patients
PDE	Pancreaticoduodenectomy
PET	Positron Emission Tomography
SA	Surgical Ampullectomy
SO	Sphincter of Oddi
Std. Deviation	Standard Deviation
Q1	25th quartile
Q3	75th quartile

Nederlandse samenvatting

Introductie en doel thesis: Ampullaire tumoren zijn tumoren in de regio van de papil van Vater, die goed- of kwaadaardig kunnen zijn. De meeste voorkomende goedaardige ampullaire tumor is gekend als een 'ampulloma'. Zij worden gezien in 0.04 - 0.12% van de algemene populatie. *Ampulloma's* kunnen voorkomen als spontane laesies of in de context van familiale adenomateuze polyposis. De leeftijd van de patiënten ligt tussen de 40 tot 87 jaar en men vindt *ampulloma's* evenveel in vrouwen als in mannen. Ampullaire adenomas zijn vaak asymptomatisch en worden per toeval gevonden bij endoscopie. Door hun locatie, kunnen *ampulloma's* toch de ampulla blokkeren. Zo geven ze dus aanleiding tot symptomen zoals geelzucht, cholangitis, dyspepsie, pijn, epigastrisch ongemak (misselijk en braken), anorexie en gewichtsverlies. Omdat deze *ampulloma's* kwaadaardig kunnen worden, worden ze behandeld ofwel endoscopisch ofwel chirurgisch. Deze thesis onderzoekt beide behandelingen met de focus op kwaliteit van leven.

Methodiek: De populatie werd gerekruteerd van de afdeling Hepatobiliaire Heelkunde in het Universitair Ziekenhuis te Gent. Na een grondige literatuurstudie werd een vragenlijst opgesteld. Deze vragenlijst werd dan door de geselecteerde patiënten ingevuld. De data uit de vragenlijst en uit het dossier van de patiënten (na informed consent) werden in een database ingegeven en statistisch verwerkt.

Resultaten en discussie: De grote obstakels voor endoscopie om chirurgie te vervangen zijn de volgende: risico op incomplete resectie, pancreatitis en bloedingen. Hoe wordt er met deze problemen omgegaan? Geeft de endoscopie, ondanks deze obstakels een betere kwaliteit van leven na de ingreep? Door de kleine steekproef waren echte statistische vergelijkingen niet mogelijk. Onze bevindingen, ondanks verschillende limitaties, komen meestal toch overeen met de literatuur en bewijzen dat endoscopie een betere kwaliteit van leven geeft, al zijn er nog wel veel complicaties. Toch heeft lokale chirurgie ook zijn eigen complicaties en limitaties waardoor het moeilijk is een definitieve keuze te maken tussen de twee opties.

Conclusies: Voor nog meer verbetering in therapiekeuze en ook in de kwaliteit van leven na de procedure, is er nood aan meer studies rond kwaliteit van leven, incomplete resectie percentages en de factoren geassocieerd met het opnieuw ontwikkelen van een *ampulloma*. Ook een langere follow-up zou kunnen helpen met het bepalen van morbiditeit en lange termijn uitkomsten. Al de resultaten van zulke studies zouden kunnen leiden tot het vormen van 'guidelines'. Deze 'guidelines' zouden dan uiteindelijk structuur kunnen geven aan het proces en klinische beslissingen makkelijker maken.

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Abstract

Introduction and objectives: Ampullary tumours are benign or malignant tumours in the ampulla of Vater. *Ampullomas* or ampullary adenomas are the most common benign ampullary tumours. They can be found in 0.04 - 0.12% of the general population. They may occur as sporadic lesions or in patients with familial adenomatous polyposis. Patients range in age from 40 to 87 years and the sexes are equally affected. Ampullary adenomas are often asymptomatic and incidentally discovered on endoscopy. However, because of its location, an *ampulloma* can block the ampulla. This can lead to the development of obstructive jaundice, intermittent cholangitis, dyspepsia, pain, epigastric discomfort (nausea and vomiting), anorexia and weight loss. Since these *ampullomas* can turn malignant, they are treated endoscopically or by performing a local ampullectomy. In this thesis, the advantages and disadvantages of both treatments are researched with the focus on quality of life.

Methods and materials: The population was recruited from the Hepatobiliary Surgery department from the University Hospital in Ghent. After a thorough literature study, a questionnaire was formed. This survey was then filled out by the selected patients. The obtained data from the survey along with the data from the patients' records (after informed consent) were statistically processed.

Discussion and results: The major obstacles for endoscopy to replace surgery is the risk of incomplete resection, pancreatitis and bleeding. How are these problems managed? Does endoscopy result, despite the obstacles, in a better quality of life?

Because of the small sample size, real statistical testing couldn't be done. Our findings, despite the limitations (such as small sample size,..), concur mostly with the literature and state that endoscopic papillectomy results in a better quality of life, but it still has a lot of complications. However, surgical ampullectomy has its own complications and limitations, which makes it difficult to definitely make a choice between the two approaches.

Conclusions: For further improvement in the treatment choices and the quality of life after the procedures, we advocate for more studies involving quality of life, recurrence rates, factors associated with this recurrence, complications and incomplete resection rates. Also, a longer follow-up duration could help with determining the morbidity and long-term outcomes. All the results of such studies could lead to the formation and development of guidelines. Lastly, these guidelines could produce a structure and/or flowchart for making clinical decisions. This could make clinical decisions easier.

I. Introduction

1.1 Ampulloma

Ampullary tumours are benign or malignant tumours in the ampulla of Vater. (1, 2, 9, 12) The most common benign ampullary tumours are ampullary adenomas or *ampullomas*. Thus, *ampullomas* refer to adenomas arising from the ampulla. (17-19) *Ampullomas* were first described in 1895 by Calzavara and they are rare neoplasms that occur sporadically or in the context of familial adenomatous polyposis. (6) One of the possible causes of developing neoplasms in this area is that the ampullary region contains a transition from pancreatobiliary to intestinal epithelium and such areas of transition are inherently unstable. (12)

1.1.1 Anatomy

The ampulla of Vater, named after Abraham Vater (1684-1751) (13) and also known as the major duodenal papil, is the place where the common bile duct (CBD) and the pancreatic duct (duct of Wirsung) merge and discharge their fluids into the duodenum. (14) Sometimes, there is an accessory pancreatic duct (‘duct of Santorini’) and this results in a minor duodenal papil. (see 1.1.1.1) (**Fig 1 & 2)**

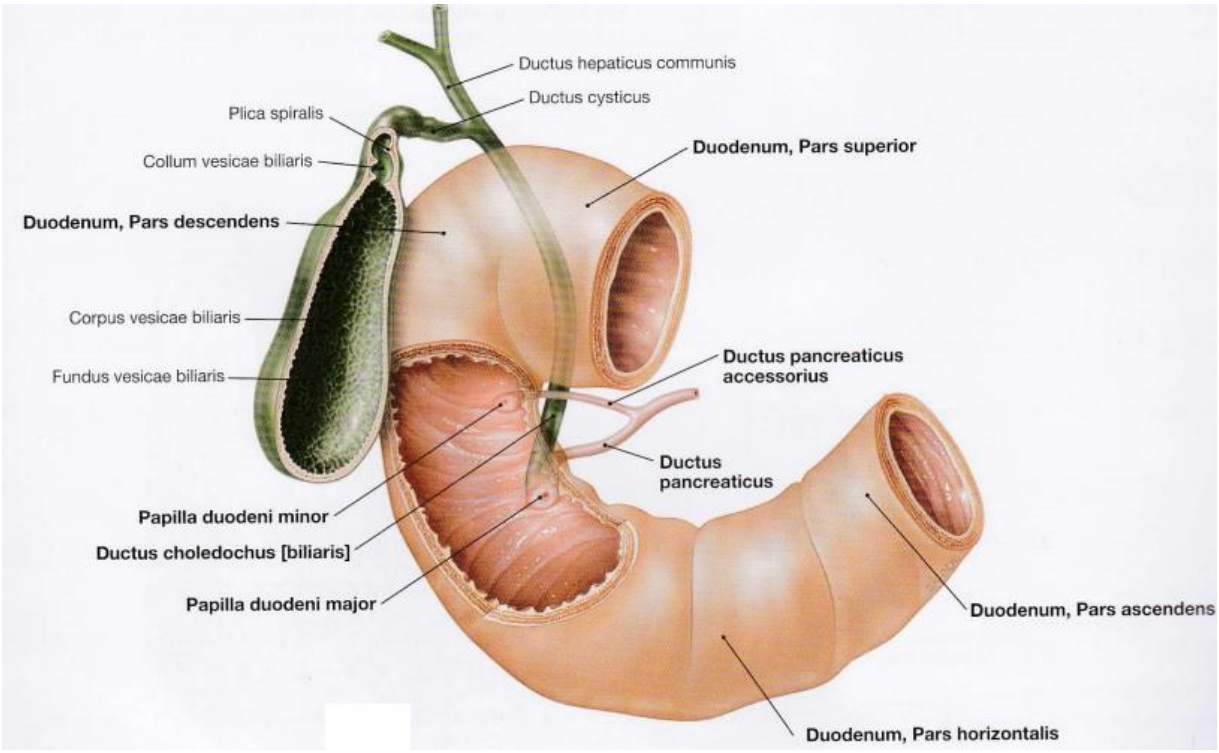


Fig. 1 The localisation of the papil of Vater (major duodenal papil) and the minor duodenal papil (15)

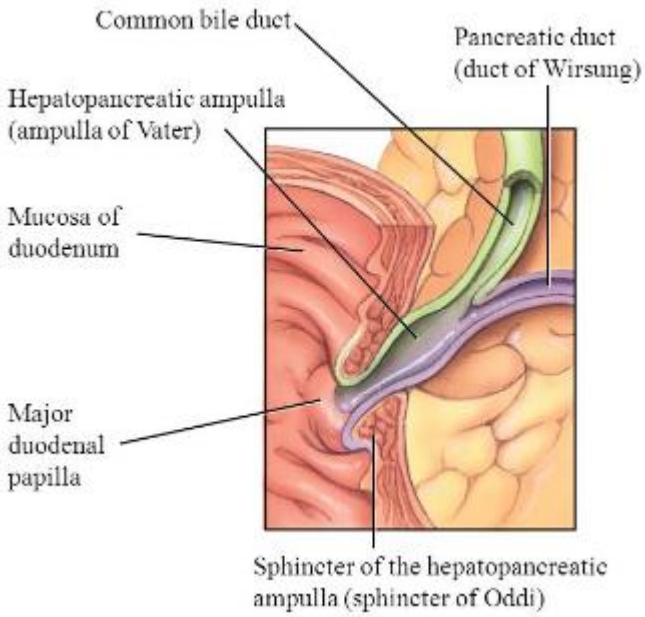


Fig. 2 Detail papil of Vater (16)

1.1.1.1 Embryology of the ampulla

The human pancreas and the gallbladder arise from the hepatic diverticulum in the fourth week of embryonic development. The gallbladder and cystic duct are formed from the caudal superior bud of the hepatic diverticulum and the ventral pancreas develops from the inferior bud. The formation of the common duct with the recanalization begins at the end of the fifth week and grows slowly, until the lumen of the common duct extends into the cystic duct by the seventh week. (17) In the seventh week, the formation of the pancreas itself starts. This formation begins with the fusion of two pancreatic primordia, one dorsal and one ventral. Each of these two primordia contains a duct, leading to the duodenum. After fusion, the distal part of the main duct of the pancreas (‘duct of Wirsung') is formed from the duct of the ventral pancreas and its proximal part from the proximal portion of the duct of the dorsal primordium. The distal portion of the embryonic dorsal pancreatic duct often regresses. However, in many cases, this portion persists despite normal fusion of the two primordia, and sometimes there will even be an accessory pancreatic duct. ('duct of Santorini') (13, 17)

1.1.1.2 Description of the adult ampulla

The ampulla is a prominence of 5 - 10 mm in length and 5 mm in width, hidden by transverse, circular, duodenal folds. The smoothing out of these folds allows the identification of the papilla. However, the papilla is also covered by a transverse fold or "hood." Below the papilla, one or more longitudinal folds hold the papilla itself downward. These folds form an

essential identification point because they are the only vertical structures in the duodenal mucosa. The apex of the papilla is usually formed by a single orifice where the biliopancreatic secretions discharge into the duodenum. The existence of this single orifice is evidence of the existence of a common channel. (This is the case in 55–86% of the individuals). The length of this common channel is influenced by the angle of the common duct into the duodenum wall. Dowdy *et al*. reported that the length of the common duct is 1 – 12 mm, with an average length of 4.4 mm. The diameter of the common duct is 1 – 4 mm, with an average of 2.6 mm. When two orifices are present and there is no common channel, the biliary opening is always dorsal and cranial in relation to the main pancreatic duct. The main pancreatic duct is usually easily identifiable. (14)

1.1.1.3 Localisation ampulla in the duodenum

The ampulla is usually located at about 8 cm distal to the pylorus inside the descending limb of the duodenum. According to the discussion of Lindner *et al*. the major duodenal papilla is mainly located in the descending part of the duodenum (in 82% of the cases) and occasionally in the transition between the descending duodenum and horizontal (in 12% of the cases) part or in the horizontal part (in 6% of the cases). (14)

1.1.1.4 Mucosa and muscle tissue in the ampulla

Obviously, the mucosae of the duodenal papilla and common duct consist of different papillary structures. The duodenal papilla lacks muscularis mucosae and a submucosal layer like the gallbladder and bile duct, but the ampulla is surrounded by the sphincter of Oddi (SO). The SO is composed of small circular and longitudinal smooth muscular tissue. (18) It acts independently of the muscularis propria of the duodenum and most of it is dispersed under the mucous membrane from the unique muscle layer, although variations exist according to Suda *et al.*

According to Suda *et al*. the sphincter of Oddi has three major functions:

1. regulation of bile and pancreatic flow into the duodenum
2. diversion of hepatic bile into the gallbladder
3. the prevention of reflux of the duodenal contents into the pancreaticobiliary tract (18)

Boyden *et al.* divided the SO roughly into the sphincter choledochus, the sphincter pancreaticus and the sphincter ampullae. According to Suda *et al*., the sphincter choledochus is best developed and regulates the outflow of bile and prevents free communication between the bile and pancreatic ducts. (14)

The basic SO pressure is 4 – 5 mm Hg higher than that of the bile duct and it controls the flow of bile from the bile duct into the duodenum and brings bile into the duodenum by peristaltic contraction. The flow of bile is affected by the total volume of bile secreted by the liver, gallbladder contraction and SO pressure. Moreover, the SO prevents the reflux of duodenal and pancreatic juice as well as bile into the cystic and pancreatic ducts. Cholangiography can visualize the movement of the sphincter peristalsis. First, the sphincter choledochus - the upper part of the SO - opens starting from the cranial end and the contrast enters the ampulla. Then, the sphincter choledochus contacts, again from above downwards, isolating a small portion of contrast in the ampulla. The distal sphincter opens and the systolic volume falls into the duodenum (opening phase). Thereafter, the distal sphincter contracts again, this time starting from the caudal end – an antiperistaltic movement. First the distal sphincter is closed, followed by the sphincter choledochus. When the contraction is complete, no contrast is seen in the intramural part and the contracted muscle produces a convex stop of the contrast in the lower common duct. (closing phase) (19)

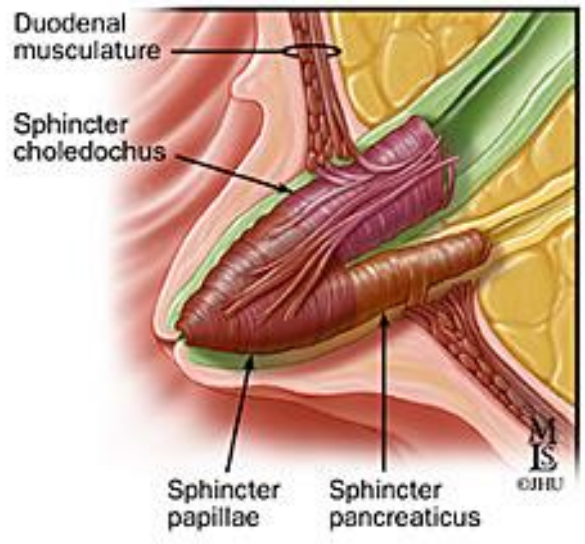


Fig. 3 Sphincter of Oddi (20)

1.1.1.5 Innervation of the biliary tract

The biliary tract is controlled by the autonomic nervous system, the celiac ganglion and the vagal nerve, which are parts of the sympathetic and parasympathetic nervous systems, respectively. A nerve that branches from the hepatic nerve plexus, formed by the sympathetic and vagal nerves, is dispersed to the gallbladder, the bile duct and duodenal papilla and controls the biliary tree. A nerve branch from the superior mesenteric plexus controls the lower side of the bile duct and duodenal papilla. (14)

1.1.1.6 Vascular supply of the ampulla

The arterial vascularisation is quite complex. There are three arteries that are important:

1. The superior posterior pancreaticoduodenal artery. This artery gives off several branches to the CBD.
2. The superior anterior pancreaticoduodenal artery, that gives off branches distributed to the duodenal wall in front of the terminal bile duct. One branch, traversing the duodenal wall near the upper border of the window, is arranged along the anterior border of the papilla. The two anterior and posterior axes are joined at the tip of the papilla by a finely anastomosed submucosal plexus (hence the hemorrhagic nature of juxtapapillary tumours)
3. The inferior pancreaticoduodenal artery, that gives off some branches to participate in the juxtapapillary submucosal network

The small caliber of these vessels results in little concern with regard to the risk for hemorrhage on sphincterotomy. However, if the margins of the duodenal window are transgressed, there is a risk for hemorrhage, because the vessels of greater caliber flow here, explaining the risk in local excisions. (14)

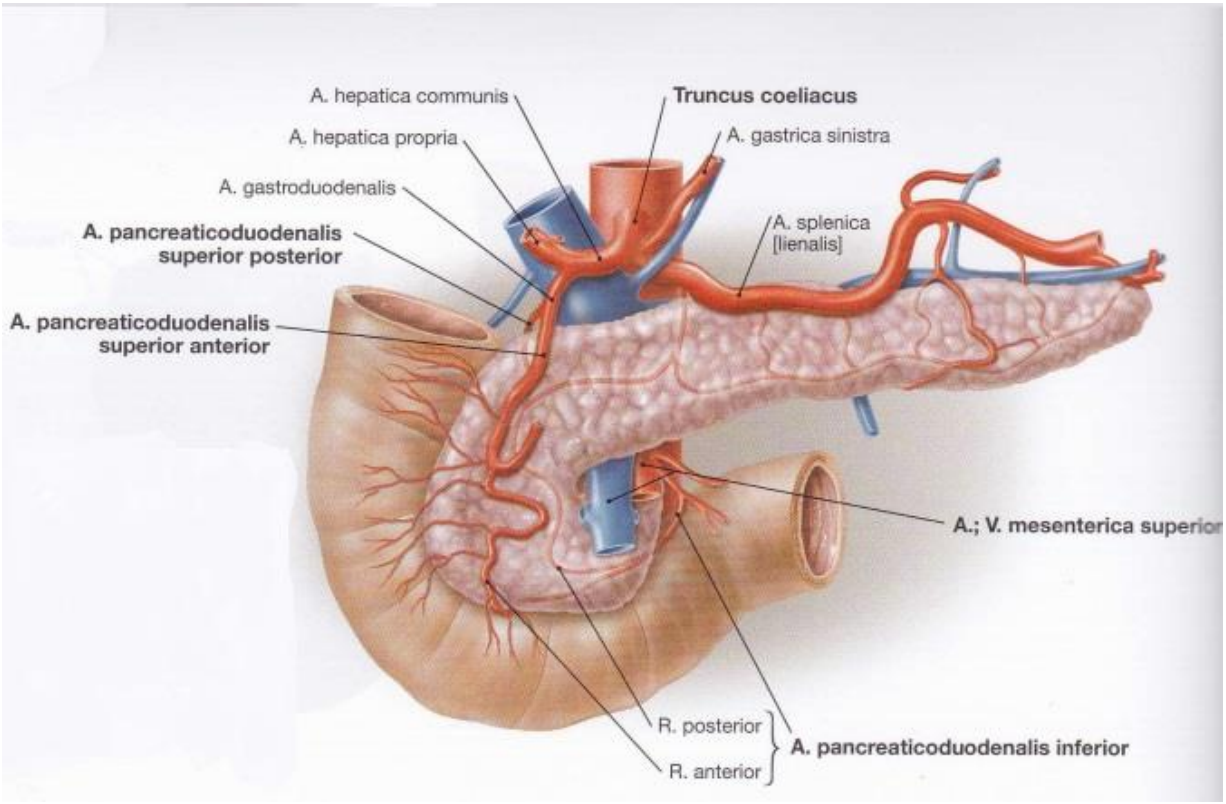


Fig. 4 Vascularisation (15)

1.1.1.7 Lymphatic drainage of the ampulla

The lymphatic drainage of the papilla is common to that of the pancreas.

1. Anterior superior territory: the lymphatic pathways travel in the right retropancreatic process to reach the splenic lymph nodes and the right interceliomesenteric lymph nodes
2. Inferior cephalic territory: it drains to the right interceliomesenteric nodes bilaterally suprarenal and infrarenal, still in the right retropancreatic process
3. Posterior superior territory: drains toward the retrocholedochal lymph nodes and then relays to the aorticocaval nodes. Numerous variations exist, with the possibility of long collectors draining the lymph of the duodenum or pancreas directly to the juxta-aortic nodes or even the left lumbar trunk or thoracic duct. (14)

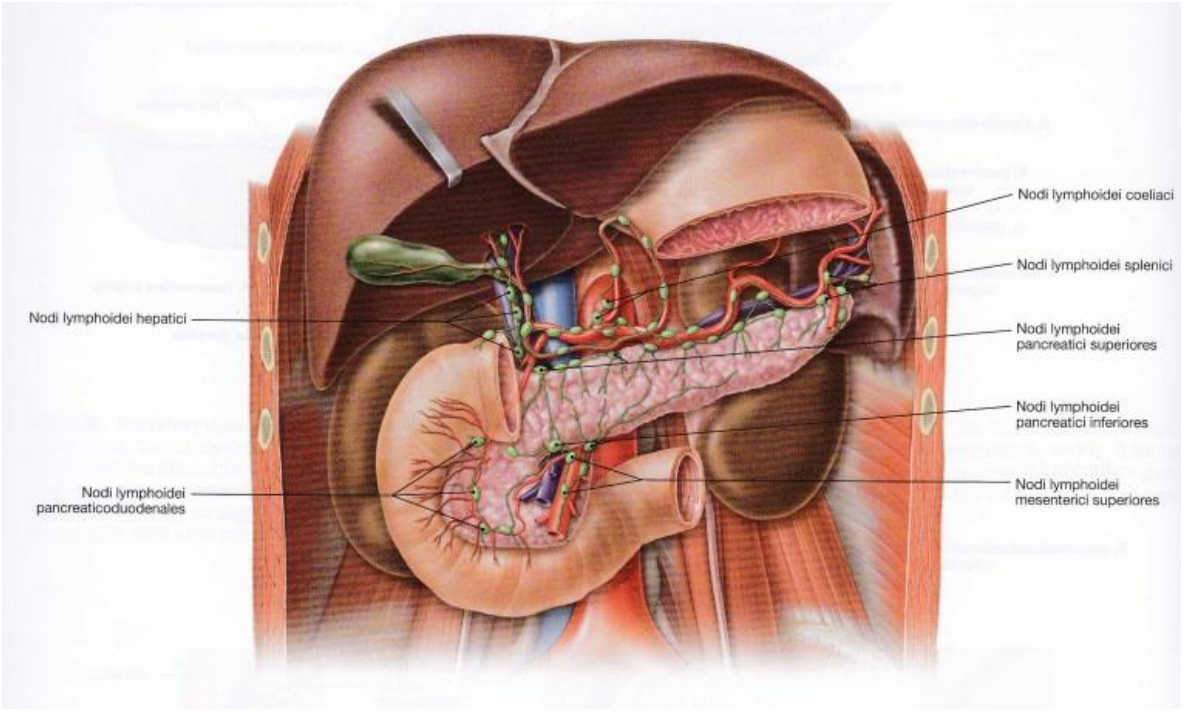


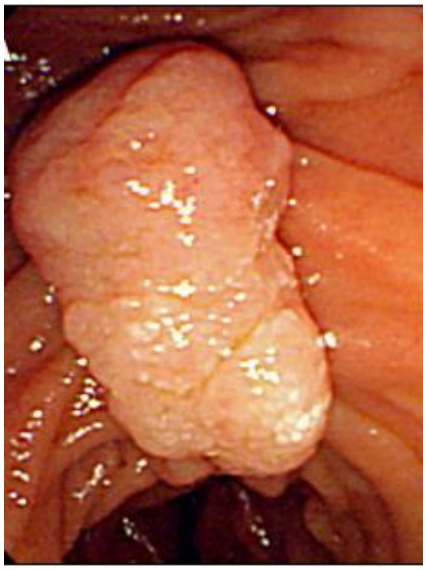
Fig. 5 Lymphatic drainage (15)

1.1.2 Epidemiology

Ampullary tumours represent 1 - 5 % of the gastrointestinal tract tumours with an incidence of 6 per million per year. (1, 8, 21-23) *Ampullomas*, the benign ampullary tumours, can be found in 0.04-0.12% of the general population. (2, 3, 5, 6, 8, 11, 12, 24-29) They may occur as sporadic lesions or in patients with familial adenomatous polyposis. (2, 5, 9, 24, 30, 31) Patients range in age from 40 to 87 years and the sexes are equally affected. (3, 5, 11, 25, 29, 30) Relevant lesion characteristics include an estimate of size by endoscopic view,

histopathologic size and the presence of intraductal extension as viewed by endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). (30, 32)

Furthermore, adenomas are considered precancerous lesions because of the *adenoma-carcinoma* sequence, similar to colon adenomas. (2, 3, 5, 8, 21, 22, 24-26, 33-37) They have a risk of transformation to adenocarcinoma of 25% up to 85%. (3, 5, 11, 25, 29, 30) However, the time frame for this transformation isn't well established. (25) Still, because of their malignant potential, resection is recommended. (2, 3, 5, 9, 10, 25, 29, 30, 33-35, 38)



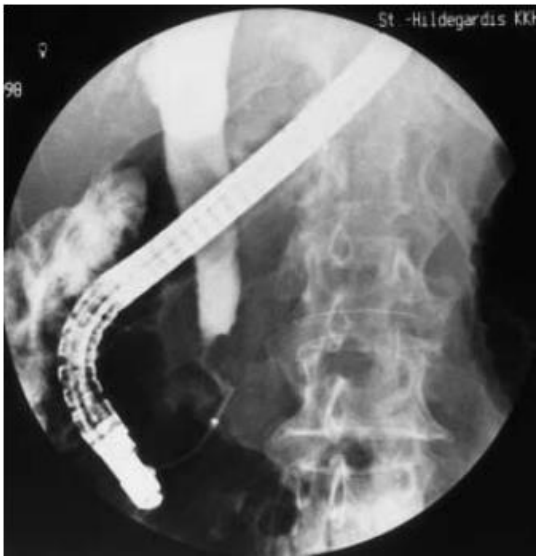


Fig. 6 *Left* Endoscopic view of adenoma arising from the major duodenal papilla (32)
Fig. 7 *Right* Endoscopic retrograde cholangiopancreaticography with dilated bile duct (18)

1.1.3 Symptoms

Ampullary adenomas are often asymptomatic and incidentally discovered on endoscopy. (24) However, because of its location, an *ampulloma* can block the ampulla.. This can lead to the development of obstructive jaundice, intermittent cholangitis, dyspepsia, pain, epigastric discomfort (nausea and vomiting), anorexia and weight loss. (1, 6, 8, 11, 21, 24, 27, 37)

So, even though ampullary villous adenomas are rare, they should be included in the differential diagnosis in any patient with anemia and obstructive jaundice. Cholelithiasis, choledocholithiasis, hyperamylasemia or pancreatitis may accompany these tumours. (27)

1.1.4 Diagnosis

The diagnosis of a tumour is done by clinical presentation (if the *ampulloma* is symptomatic) or when a mass is found by coincidence.

When the *ampulloma* is symptomatic, a blood analysis can be done. (routine blood analysis with blood cell count, electrolytes and serum liver enzyme assays: serum albumin, aspartate

aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, direct/indirect/total bilirubine, gamma-glutamyl transpeptidase (GGT)) These lab results mostly show elevated levels of bilirubin, AST and ALT. (39) However, these lab results are indicative of an obstruction and not of a tumour, so further exploration is needed.
It is difficult to achieve an accurate diagnosis and exclude malignancy based on preoperative studies because of the possibility of an invasive carcinoma within an adenoma. (40) In most studies, it was described that the patients frequently had an endoscopy, ERCP, EUS and contrast enhanced computed tomography (CECT) to diagnose the *ampulloma*. (1, 6, 8, 11, 12, 21, 22, 36, 38, 41)

On the endoscopic view, ampullary adenomas are typically discoloured soft lobular lesions, whereas firmness, ulceration and duodenal wall adherence are present in malignancies with local invasion, but this isn't always easy to differentiate. (11, 21, 24) So, on the basis of endoscopic appearance alone, ampullary adenomas cannot always be distinguished from ampullary carcinomas or non-adenomatous polyps (carcinoid tumours, gangliocytic paragangliomas, etc.). (9, 33, 42) Detection of microscopically invading malignant foci in the main adenoma or intraductal invasion on the other hand, can also prove to be difficult in some cases. (21, 32) Thus, a definitive tissue diagnosis is a prerequisite for appropriate management, but the false negative rate of forceps biopsy for the detection of infiltrating carcinomas is not uncommon (16 - 60%). (3, 9, 24, 25, 32, 33, 36, 42, 43) To overcome this difficulty, some authors propose a more extensive diagnostic and therapeutic use of papillectomy instead of a forceps biopsy: the quality of the histological specimens may be better, the pathological diagnosis more accurate and the need for new biopsies significantly reduced. (9, 33, 42) In short, an endoscopic papillectomy can be needed to gain sufficient tissue for complete histopathologic examination to overcome the limitations of forceps biopsy. (9)

Aside from regular endoscopy, ERCP, EUS, and intraductal US can provide useful information in the assessment of ampullary adenomas. ERCP permits assessment of the degree (if any) of intraductal extension of the adenoma and it shows obstruction if there is any. EUS and intraductal US may also identify malignancy and permit evaluation of its extension beyond the muscularis propria (depth lesion as locoregional lymph node status). (9) EUS has been found to have an 83% and 72% diagnostic accuracy for predicting malignancy and resectability, respectively. Finally, (CE)CT can also identify possible regional lymph node metastasis. (11)

EUS has been shown to be superior to CT, magnetic resonance imaging (MRI) or transabdominal US for tumour staging. Intraductal ultrasound has demonstrated superior accuracy over EUS for local T-staging and intraductal extension. (3, 9, 23, 24) Unfortunately, intraductal US is not everywhere available. (9, 24) However, CT scan, MRI, and positron emission tomographic (PET) scans are highly sensitive for the detection of distant metastases. In the assessment of nodal involvement, MRI has been found to be superior to both CT and EUS. (42) Although in the end, both MRI and EUS are limited in their ability to distinguish between early malignant adenocarcinoma and benign adenoma, so exact diagnosis in an early stage before resection is very difficult, even after performing intraductal ultrasound. (9) Another problem is that there are insufficient data on lymph node metastasis. (9) However, from a surgical perspective, Lee *et al*. reported neither lymphovascular invasion nor lymph node metastasis in surgical specimens of patients with adenoma of high grade dysplasia. (31) Factors associated with an increased risk of lymph node metastasis included tumour size, poor histologic grade, perineural invasion, microscopic vascular invasion, as well as depth of invasion/T stage. (28)

In conclusion, there is currently no consensus about the preprocedural staging protocol. (35)

1.1.5 Histology

The prognosis depends on histological typing of the tumours and their clinical stage. (1, 2) So, in terms of histopathological classification of neoplasmatic lesions of the ampulla of Vater, 40% are tubulovillous adenomas, 30% villous adenomas, 10% tubular adenomas and 20% are nonepithelial lesions such as endocrine adenomas or neurinomas. (6) The two forms of villous tumours, sessile and pedunculated, ranging in diameter from 4 mm to 7 cm have already been described. (27)

In accordance with the Vienna classification criteria of gastrointestinal epithelial neoplasia, ampullary lesions were categorized as low grade dysplasia adenoma, advanced adenoma (moderate dysplasia), adenoma with high-grade dysplasia and adenocarcinoma. (5, 30) At present though, a classification system for ampullary lesions based on endoscopic morphology does not exist, which makes clinical decisions difficult. (38)

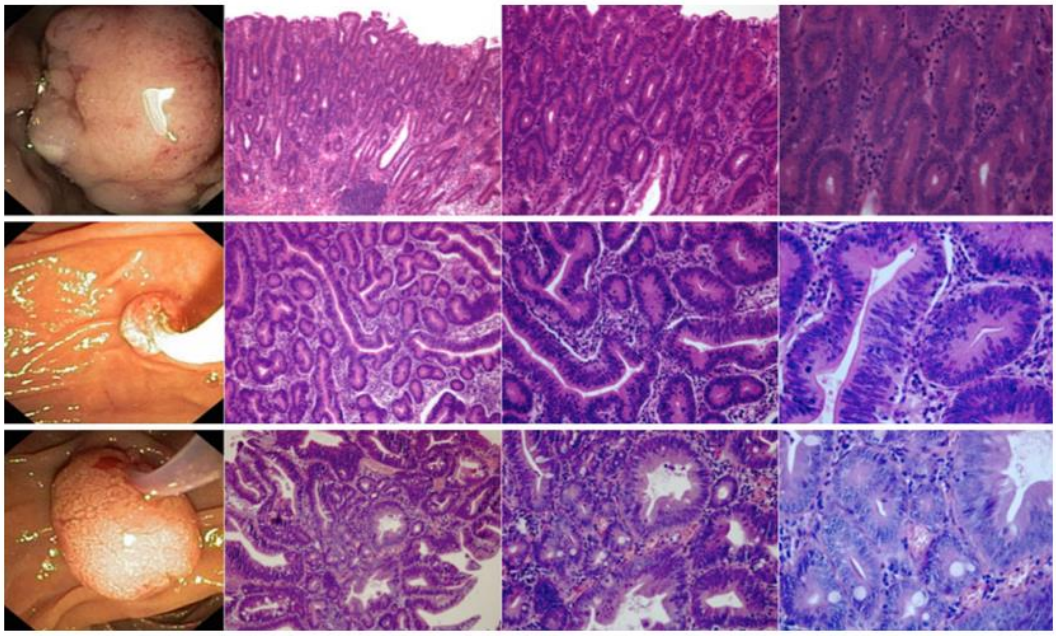


Fig. 8 Macroscopic and microscopic appearance of ampullary tumours of the papilla. *Top row* Tubular adenoma with low grade dysplasia [macroscopic view, hematoxylin and eosin (H&E), original magnification 9100, 9200, 9400]. The glands reveal a relatively uniform shape and size. Slender and hyperchromatic nuclei show slight variation in size and shape. *Middle row* Tubular adenoma with high grade dysplasia (macroscopic view, H&E, original magnification 9100, 9200, 9400). The glands exhibit irregular arrangement. Cellular atypia is more prominent. *Bottom row* Tubular adenocarcinoma (macroscopic view, H&E, original magnification 9100, 9200, 9400) The glands show papillary and irregular tubular structure and have variable size and shape with marked atypia (2)

1.1.6 Therapy

Treatment possibilities include endoscopic papillectomy (EP), surgical transduodenal excision (surgical ampullectomy or SA) and pancreaticoduodenectomy (PDE or Whipple). (1)

It is important to remember that the term ‘‘ampullectomy’’ refers to the removal of the entire ampulla of Vater and that it is a surgical term for procedures which require surgical reimplantation of the distal CBD and pancreatic duct within the duodenal wall. Technically, when endoscopic resections of lesions at the major papilla are performed, only tissue from the papilla can be removed endoscopically, and thus the term ‘‘papillectomy’’ is more appropriate than the term ‘‘ampullectomy’’. Although, the two are often used interchangeably in the literature. (9, 24, 42)

A procedure is called successful when a complete resection has been reached. A complete resection means that when a patient undergoes a surveillance endoscopy and there is no endoscopic evidence of persistent abnormal tissue -with or without surveillance biopsies- at any time after the primary procedure. (9)

1.1.7 Prognosis

As previously said, the prognosis of *ampullomas* depends on histological typing of the tumour and their clinical stage. *Ampullomas* are associated with an excellent prognosis and if the tumour is limited to the duodenal mucosa without any invasion into the adjacent pancreas, then the five-year survival may be as high as 90%. (1) If the tumour is not limited to the duodenal mass, then it is called a peri-ampullary tumour. Peri-ampullary tumours are neoplasms that arise within 2 cm of the major papilla in the duodenum. They can originate from the pancreas, duodenum, distal CBD or the structure of the ampullary complex. Although the surgical approach of ampullary and peri- ampullary tumours is similar, ampullary and duodenal tumours have a better prognosis than the peri-ampullary tumours. (18) Ampullary tumours are often more resectable than other peri-ampullary neoplasms because they are usually diagnosed in an earlier stage and have a better long-term outcome after resection. (28) Hence, differentiating a true ampullary neoplasm from a peri-ampullary neoplasm is essential. The distinction between an ampullary and peri- ampullary neoplasms might be achieved by MRI. (18)

Occasionally, ampullary adenoma can recur as invasive adenocarcinoma after local excision. Therefore, some researchers advocate radical resection, meaning PDE, even for benign ampullary tumours. In contrast, several reports have been issued on the safe application of local resection in ampullary adenoma with low recurrence rate. (36) This will be further discussed below.

1.1.8 Follow-up

A standard protocol for non-ampullary and ampullary tumour surveillance is not settled. In some authors' opinion, endoscopic imaging that can target an adenoma is the most practical way for endoscopic surveillance. (9, 44) Catalano *et al*. outlined some guidelines to perform endoscopic treatment every 2 – 3 months until there is no residual adenoma with surveillance every 6 – 12 months for the next 2 years. If recurrence is not identified, further patient follow-up should be individualized. (3, 11, 29)

1.2 Endoscopic treatment

Endoscopic papillectomy (EP) was first performed in 1983 by Suzuki *et al*. using laser photoablation and, soon thereafter, by snare resection by a group in Lyon, France. (25) Since then, various authors have described their techniques and overall success. (11) Endoscopic resections, as we know them now, were first reported by Binmoeller *et al*. in 1993. (3, 12)

Now, EP is increasingly used as the first line approach to resection for ampullary adenomas. (9, 10, 35, 45, 46) It is rapidly replacing classic surgical resection and is a less invasive procedure. (9, 10, 24, 42, 47) The technique is recognized as a safe and reliable treatment for benign lesions. (3, 9-11)

1.2.1 Technique

Techniques for the endoscopic removal of ampullary adenomas remain non-standardized, probably due to the relatively small number of procedures of this type. (9, 24) Furthermore, there is no uniform agreement on the terminology used to describe various resection modalities. (24, 41, 47)

Endoscopic papillectomy is performed using routine intravenous conscious sedation and a side-viewing therapeutic duodenoscope under fluoroscopic guidance. So, ERCP is performed first to identify lateral spread onto the periampullary duodenal wall and identify access to each duct (biliary or pancreatic) and then exclude invasive growth into either or both ducts. After this evaluation, submucosal injection can be performed (choice of the endoscopist). The main ampullary lesion is then ensnared, applying the snare in a top down fashion to avoid excessive tissue capture and perforation. The lesion is excised using a blended, electrosurgical cutting current ("Endocut") to avoid excessive coagulation injury and development of stenosis of either duct. Sphincterotomy is sometimes required to visualize intra-ampullary lesions. Lesions not amenable to *en bloc* resection are excised in a piecemeal fashion. Immediately following resection, the site is inspected for any visible residual tumour and bleeding. Sometimes, a pancreatic stent was placed after sphincterotomy with the intent of decreasing postendoscopic retrograde cholangiopancreatography pancreatitis or obstruction. Patients are not routinely monitored overnight for complications, unless they experienced postprocedural abdominal pain. All patients are assessed prospectively for complications at 24 – 48 h and at 1 month by an experienced clinical nurse coordinator. (24, 41, 47)

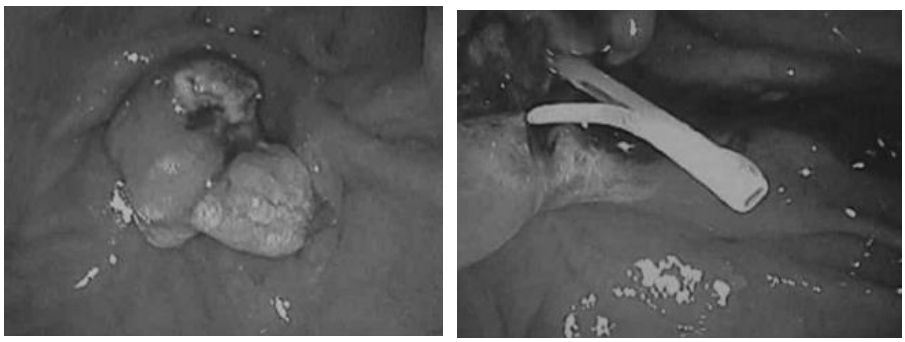


Fig. 9 *Left* Benign ampullary lesion before endoscopic resection, *Right* Pancreatic duct stent placed prophylactically after endoscopic resection (37)

1.2.2 Indications

The indications for EP are still not fully established. One absolute indication is an adenoma confined to just the ampullary region (not in Oddi's sphincter), absence of extension into the pancreatic or biliary ducts, no evidence of malignancy, no invasion of the duodenal muscular layer and with a size less than 4 cm. (2, 10, 25, 32, 33, 36, 42) The lack of symptoms makes the success of an endoscopic resection much more likely, because symptoms suggest some element of biliary or pancreatic ductal obstruction either from intraductal extension of the neoplasm. (11) Also, the size cutoff for EP has been previously reported as 4 cm. However, this seems to be arbitrarily assigned from previous descriptions of EP for malignant ampullary lesions less than 4 cm and benign ampullary lesions up to 7 cm in size. In fact, the size has failed to show any correlation with the presence or absence of malignancy or with proximal duct extension. Gross and anatomic features of the neoplasm during the initial endoscopic investigation before resection seems to be more important than the size in the prediction of malignancy. Anatomic features seem to be more consistent and reproducible as criteria to distinguish benign from malignant pathology. (4, 11)

As to be concluded from the previous, the indications for EP are still being formed and techniques are evolving. The application of piecemeal resection for example resulted in a gradual increase in the size of the tumour resected. Intraductal extension less than 1 cm does not seem to be an absolute contraindication for EP, because the tumour can be exposed to the luminal side with balloon sweeping and, thus, resected completely. (5, 24)

Lastly, there is no consensus as to which ampullary adenomas should be kept under surveillance and which lesions should be removed endoscopically or surgically. Several authors have advocated that endoscopic resection should only be performed in patients without evidence of invasive cancer. Although endoscopic removal of ampullary adenocarcinoma has been described, this should not be endorsed for routine management. (5, 24, 25, 46)

1.2.3 Advantages

Previous data concluded that EP has an efficacy with lower morbidity (18% vs 42% for surgical ampullectomy) in properly selected patients. (2, 11, 30, 31, 44) EP is a less invasive treatment than surgery which shows itself in shorter hospitalization and lower mortality rates (0.4% vs 0-9% for surgical ampullectomy). (5, 32, 42, 44, 45) Several studies have reported that the endoscopic resection of ampullary adenomas was successful in 75-90% for adenomas

without intraductal extension and about half as successful even when some intraductal extension is present in the patients. (10)

1.2.4 Disadvantages

From before, it can be concluded that there are still many questions about aspects of current EP such as indications, standardized technique (power settings for electrosurgical units, submucosal injection, post-ampullectomy ablative therapy and prophylactic stent placement), equipment, need for prophylactic antibiotics, surveillance, prevention and management of complications. (24, 32, 42, 47) There is still a knowledge gap about the patient and lesion characteristics that are associated with the ability to do a successful endoscopy. (2, 30)

The main limiting factors for endoscopic resection as a curative intervention are incomplete removal, technical difficulties, recurrence and complications. (30, 44) Although several studies showed 15 - 20% recurrence rates and 20% to 27% complication rates, these rates are still incompletely reported. (9, 10, 30) Besides, if endoscopic resection is not successful or recurrence of the ampullary pathology occurs, a surgical approach has to be considered. The potential advantages of EP then vanish compared with PDE, which is considered as a surgical treatment option by many clinicians after endoscopic therapy has failed. (45) While endoscopic therapy has been increasingly reported, studies which assess long-term outcome with prospective assessment of endoscopic complications are limited. (3)

One may also see the contra-indications for endoscopy as a disadvantage. The contra-indication is ampullary carcinoma. The presence of high-grade dysplasia, carcinoma in situ, or obstructive jaundice is considered by many to be a relative contraindication for endoscopic resection. (6)

1.2.5 Complications

Endoscopic removal of ampullary adenomas is considered a ‘‘high-risk’’ procedure for complications, with a morbidity and mortality of 23% (range 10 - 58%) and 0.4% (range 0 - 7%), respectively. (5, 42, 45) Pancreatitis (8% to 15%) and bleeding (2% to 13%) are the most common early complications of EP. Duodenal perforation is rare, about 0% to 4%. Papillary stenosis can occur as a late complication with a 0% to 8% rate. (2, 9, 29, 32, 42, 45, 48) Bleeding is mostly mild and can be treated endoscopically using injection of adrenalin, clipping or argon plasma coagulation. However, bleeding after resection can interfere with subsequent pancreatic stenting. Delayed continuous oozing after resection requires cumbersome, time-consuming and repeated hemostasis. Cholangitis is a rare complication,

(0% to 2%) that is easily controlled by endoscopic sphincterotomy followed by implantation of a plastic biliary stent. There is no established consensus for prophylactic endoscopic sphincterotomy with biliary stenting to prevent cholangitis after EP. (2, 9, 32, 42, 45, 48) However, placement of a prophylactic pancreatic duct stent is highly recommended to reduce the risk of pancreatitis, especially for the severe form. (2, 3, 9, 32, 42, 45, 47, 48) It has also been implied that placement of a pancreatic stent during EP may minimize the risk of stenosis of the pancreatic duct orifice and may allow safer use of adjunctive coagulative therapies. On the other hand, a recent retrospective study of 82 patients suggested that routine pancreatic duct stenting may not be necessary. Others have suggested that pancreatic duct stents should be used only if pancreatic duct drainage is deemed suboptimal or if the pancreatic duct is difficult to cannulate after the procedure. (9, 29)

In conclusion, a prophylactic biliary stent is not recommended (9, 24), but a pancreatic stent after EP is. The shapes, diameters and lengths of pancreatic duct stents and the removal time are also not standardized. The removal time of such stents can vary from 2 days to 3 months. Sometimes, it is necessary for a pancreatic stent to remain in place longer to protect the pancreatic duct orifice during second procedures for the removal of remnant tissue. (32)

1.2.6 Post-procedure evaluation

A period of post-procedure in-patient observation should be considered for the detection and treatment of any immediate or slightly delayed complications. (5, 42, 45) There is no consensus about the interval, modality and method of post-EP surveillance. In cases with complete resection of ampullary adenoma, follow-up endoscopy with ERCP and multiple biopsies is recommended at 1, 3, 6, and 12 months after resection and then at yearly intervals for 5 years on obtaining a negative biopsy. (32)

1.3 Surgery

Surgical ampullectomy (SA) was first introduced by Halstead in 1899 and was initially attempted as treatment for ampulla of Vater cancer. (3, 11, 23, 49, 50) The use of this procedure failed to become widespread because the surgical technique had not been standardized and the recurrence rate was high. Since Whipple introduced pancreaticoduodenectomy (PDE) in 1935, it has been recommended as the definitive surgery for ampulla of Vater carcinoma. (6, 23, 28, 33, 37, 40, 49)

Surgery has been the traditional approach for removal of ampullary adenoma before the advances related to endoscopic therapy in the last 10 to 20 years. (36) It now remains the standard curative therapy for confirmed or suspected ampullary adenocarcinoma, although endoscopy can provide adequate palliation in patients deemed not to be surgical candidates. (9, 30, 32, 35) So, there are two kinds of surgical options for ampullary tumour: standard radical surgical resection by pancreaticoduodenectomy (Whipple) and surgical ampullectomy as a local surgical excision. (9, 30, 32, 35)

1.3.1 Technique

Only the technique of local ampullectomy is described because this thesis doesn't comprise the PDE.

Under general anesthesia, with the patient in the supine position and the surgeon standing on the patient's right side, the surgeon makes an upper midline or extended right subcostal incision depending on the patient's body habitus and previous incisions. A complete visual and manual abdominal exploration is performed upon entering the peritoneal cavity to assess for systemic spread. A self-retaining retractor suited for the exposure of the central abdomen is used to provide adequate exposure. Once the colonic hepatic flexure is mobilized, a complete Kocher (incision of the peritoneum at the right and then flect the head of the pancreas and the duodenum to the left) maneuver is performed to fully expose the posterior aspect of the duodenum and facilitate bimanual palpation of the ampulla. An approximately 4 cm longitudinal duodenotomy is made along the lateral wall of the second portion overlying the area of the ampullary tumour. Serial stay sutures (2-0 silk) are placed on either side of the duodenotomy to facilitate exposure of the ampulla **(see Fig 10).** Once the ampulla is directly visualized, the tumour is usually readily visible. (36) A cholecystectomy can be performed before this procedure to enable transcystic catheterization of the CBD. (in case of choledolithiasis,..) The catheter can be brought through the ampulla to help in identifying the bile duct during the transection. A figure of eight suture (2-0 silk) is placed directly through the mass to facilitate its lateral distraction away from the common bile and pancreatic ducts. Submucosal infiltration of the medial duodenal wall with dilute epinephrine solution is usually performed circumferentially around the tumour. Electrocautery is used to excise the mass. A needle-point electrocautery tip allows for precision and minimizes thermal injury to the bile duct and pancreatic duct. Excision begins at the eleven o'clock position. With the lesion retracted inferiorly, the electrocautery is used to cut the posterior duodenal tissues directed toward the CBD until the bile duct is encountered. Once the lumen of the CBD is

entered, a 4-0 or 5-0 absorbable suture (PDS or vicryl) is used to approximate the bile duct to the medial duodenal wall. The suture should be placed by first entering the CBD lumen, incorporating the full thickness of the CBD and medial duodenal wall and finally exiting through the duodenal mucosa. The dissection is then continued in a clockwise fashion. If the bile duct had not been previously drained, a spurt of bile will announce entry of the bile duct and facilitate visualization. As the dissection is continued, the pancreatic duct will be encountered at approximately the two o'clock position along with the effluence of clear pancreatic secretions. The pancreatic duct is approximated to the duodenal wall in the same manner as described for the CBD. It is important to maintain constant maximal lateral traction on the mass itself to facilitate obtaining a negative medial margin. Using this technique, the dissection is continued in a circumferential clockwise manner until the ampullary mass is completely excised. (resected with electrocautery lifting it off the underlying duodenal wall and maintaining a 5 mm circumferential margin) The sequential sutures placed to approximate the CBD and pancreatic duct to the duodenal wall should resemble the spokes of a wheel when excision is complete. **(Fig 11)** At this time, depending on the clinical situation, the specimen can be sent for frozen section evaluation. After the OK from pathology, the outer sutures are secured and the common walls of the pancreatic duct and CBD are approximated with two to three interrupted 5-0 absorbable sutures, placing the knot in the duodenal lumen. At this time, the excess suture material is cut and the excision and reconstruction are now complete. Visualization of biliary and pancreatic drainage confirms patency of both duct systems. Duodenal closure is performed in a transverse orientation so as to avoid narrowing the lumen. The stay sutures placed at the initiation of the procedure are removed, except for the two that are located at the midpoint of the anterior and posterior edges, thus converting the longitudinal duodenotomy to a transverse orientation. The decision to leave a closed suction drain is at the surgeon's discretion. Lastly, the fascial and skin closure is performed. (51)

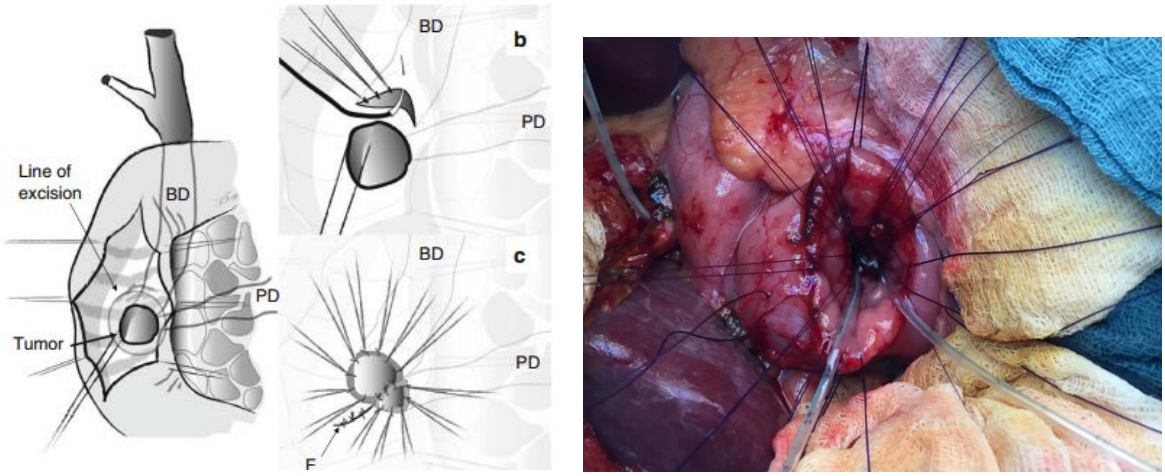


Fig. 10 *Left* Schematic demonstrating surgical ampullectomy: The duodenum wall has been opened. Stay stitches on each side hold the duodenotomy open for access. The pancreatic duct (PD) and bile duct (BD) are outlined. *Middle top row* Shows progress of the procedure. After the bile duct is identified with incision into the posterior wall of the duodenum, serial sutures are placed to approximate the bile duct to the duodenal mucosa. Traction on the tumour is achieved by pulling a stay stitch on the tumour downward. *Middle bottom row* Demonstrates the field at the end of the procedure. The re-approximated bile and pancreatic ducts are shown. Note the fold (F) shown. This is redundant mucosa that is approximated by simple stitches. (5)

Fig. 11 *Right* Operative view of an SA made in the University Hospital Ghent

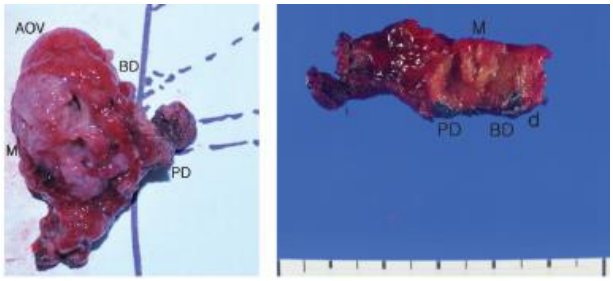


Fig. 12 Postoperative specimen *Left* specimen showing its orientation. *Right* Transected specimen with an inked margin. D = second portion of the duodenum; M = mass; PD = pancreatic duct; BD = common bile duct; d (inked portion) = ductal resection margin of bile duct and pancreatic duct. (5)

1.3.2 Indications

PDE remains in general the only choice in the case of incomplete removal and if malignancy is clearly present. (5)

Potential specific indications for surgical ampullectomy (SA) are ampullary adenomas, inflammatory or fibrotic stenosis, dysfunction of the major or minor papilla resulting in upper abdominal pain, recurrent acute pancreatitis and cholestasis. (45) SA can also be applied to larger, deeper lesions than EP and can be performed when the ampullary adenoma extends into the ampulla of Vater and further into the orifice of the main pancreatic or bile duct. Lastly, it can be applied to adenoma of the papilla with high-grade dysplasia, large (>2 cm) villous or tubulovillous adenoma of the papilla or adenoma with carcinoma in situ and other benign tumour, such as gangliocytic paraganglioma. (36)

It is important to remember to ensure complete excision with an adequate margin and it is necessary to excise the ampulla and reconstruct the CBD and pancreatic duct orifices. After tumour resection, gross and microscopic margins should be confirmed by frozen section. The careful selection of lesion of the ampulla of Vater by adequate preoperative evaluation and the use of intraoperative frozen section biopsy to assess grade of tumour differentiation and margin involvement ensures the acceptability of SA. (36)

1.3.3 Advantages

PDE has long been described as the definitive therapy for ampullary neoplasms because of the low risk of local recurrence. Thus, surgical management often allows complete removal. (24) However, in local surgical techniques recurrence does exist. Recurrence rates for SA for benign ampullary neoplasms vary widely, but more contemporary studies over the last decade report rates of 10% to 25%. (11) The advantage of SA is that it allows complete circumferential resection of the ampulla of Vater, which enables precise pathologic examination. So, compared to PDE, SA has less morbidity and mortality. Compared to endoscopy, SA has the advantage of a better resection.

1.3.4 Disadvantages

There is substantial morbidity (25%-65%) and mortality (0%-2%) associated with PDE and SA (14%-33% morbidity, 0%-9% mortality). (6, 11, 36, 49, 50) Although local surgical excision has lower morbidity compared with the PDE, limited data suggest that there is a higher (30%) risk of recurrence. (5, 24, 30, 38) The reason for the shift towards endoscopic removal of adenoma is related to the significant morbidity and mortality associated with surgery. (24, 30) Also, SA requires technical expertise and it can be considered over-treatment for a relatively small ampullary lesion. (24)

1.3.5 Complications

Complications include postoperative anastomotic dehiscence and fistulae in up to 9% and 14% of patients, respectively. (9) Other complications exist such as wound infections, cardiopulmonary complications (related to anesthesia), delayed gastric emptying, intra-abdominal collections, passage disturbance and pancreatitis (due to duct stenosis or papilla orifice stenos). (12, 40)

1.3.6 Post-procedure evaluation

Less invasive surgical options such as SA are available, but recurrence is a possibility when these less invasive surgical interventions are used. Similar to endoscopy, these patients will

also require follow-up endoscopy, whereas those who receive PDE do not require further surveillance. (24)

1.4 Algorithm treatment possibilities

Although there isn't a vast flowchart for clinical decisions, clinicians tend to follow next algorithm.

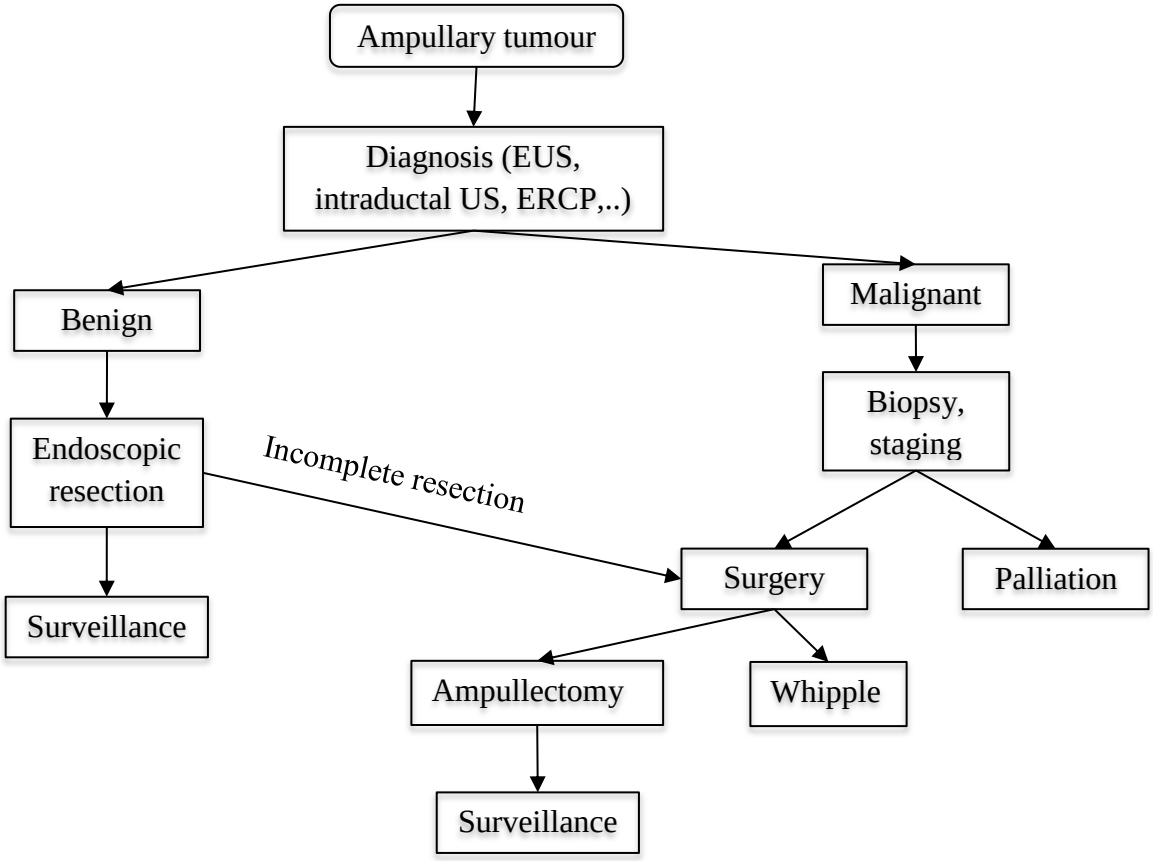


Fig. 13 Algorithm for management of an ampullary tumour

1.5 Quality of life

1.5.1 Concept

Quality of life is vague concept that is recently being used more and more. In this thesis, this concept is used because medical practitioners have traditionally focused on organic diseases and their treatment. However, patients are concerned with their symptoms, regardless of the presence of organic or non-organic findings. For patients, symptoms are indicators of disease, while clinicians have traditionally concentrated on histological or serological findings. The wider concept of health-related quality of life (HRQL) encompasses not only the condition for which the patient is treated, but also correlated morbidity and other aspects of treatment; such as side-effects that make one treatment preferable over another. Questions such as: what is quality of life, how is it measured and how can the information be used, are highly relevant in

our society where patients have become informed health consumers demanding effective treatment of their symptoms. Nowadays, patients can download information from the internet and request a particular therapy, a therapy that is disagreeing with the clinician's suggestions. Therefore, it is important to have a wider perspective when managing the patient. (52)

Now, what is this health-related quality of life? HRQL is an individual's dynamic perception of the impact of a health state upon physical, emotional, and cognitive function, social role performance, well-being, and life satisfaction. It is subjective and multidimensional. (52)

1.5.2 Purpose

The purpose of focusing on HRQL is to go beyond the presence and severity of symptoms of disease or side-effects of treatment, examining how patients perceive and experience these manifestations in their daily lives. Key and core domains reflecting HRQL are represented by physical, mental and social functioning. An individual's quality of life is influenced by socioeconomic factors (i.e. a person's financial status affects his/her housing and physical environment, and educational, recreational and cultural opportunities). If a person's income allows him/her to achieve a good nutritional status, enjoy living in the community and win the respect of his/her neighbours, job satisfaction is likely and physical and emotional well-being are promoted. Other factors determining HRQL are age, gender, disease and treatments, which will be discussed below. (52)

The quality of life results provide a basis for a holistic view of the patient and supplement the traditional outcomes. They may also document the full range of treatment benefits and possible side-effects and can predict the treatment outcome. Because gastrointestinal disorders are so prevalent, there has been an increasing need to assess the burden of these conditions using symptom and HRQL assessments, especially in the clinical setting. Even though alleviation of symptoms is generally well understood, it is not always evident that the evaluation of treatment effects requires a more comprehensive perspective. The patient's view will always be subjective and the patients' needs should be in the focus in clinical practice. Hence, patient reported symptoms and HRQL outcomes represent important end-points in clinical trials of medical treatments in gastrointestinal diseases. More comprehensive outcome assessments are required to determine the effectiveness of new treatments for functional gastrointestinal disorders. These should be based on a combination of clinician and patient reported assessments. Health utility scores are also essential components of cost-utility analyses. These analyses can influence reimbursement decisions for treatments. (52)

1.5.3 Measurement

Patient reported outcome measures need to satisfy certain sets of psychometric criteria, as these are used to describe the burden of illness or used as end-points in clinical trials. The SF-36 and the SF-12 are widely used in gastroenterology and enables general comparisons between different patient groups. The generic instruments include a broad range of aspects such as physical, emotional and social functioning, role performance and perceived health. They are therefore less sensitive to changes in specific symptoms but more reliable in addressing their general impact on a wide range of daily activities, mental health and functioning. However, the outcomes of quality of life measurements depend on several factors such as :

1. Gender: Several indexes have shown to have different results in men and women and across different age groups, in the general population as well as in different patient populations. Female individuals were found to have an overall lower score of well-being than males in a normal population.
2. Age: Age is an important factor reflected in quality of life measurements in different age groups. HQRL appears to be affected by the phase in life an individual has reached. Evaluations have shown that middle-aged individuals have lower values than optimistic young and older patients.
3. Expectations: A patient's emotional status regarding his/her expectations or hope of improvement has a profound effect on HRQL.
4. Severity of symptoms: Overall symptom severity is well reflected in the HRQL evaluations. This may be a result of multiple aspects of anxiety concerns, social situation etc. In studies where HRQL scores have been compared with symptoms obtained by asking questions, there has been a good correlation between symptoms and scores.
5. Disease and disabilities: Disease and disabilities may dramatically influence several of the variables. In some cases, they result in socioeconomic deterioration and emotional crises, with loss of one's job, friends and sexual partners. In others, the support from friends, neighbours and colleagues may actually increase the positive effects of several of these aspects.
6. Effect of treatment: Treatment is yet another factor of importance, not only the effect on the specific disease treated, but also the side-effects seen with treatments. Good examples of this are side-effects of oncology drugs, where survival, toxicity and the impact of functional status may vary according to the individual's phase of life. (52)

II. Materials and methods

2.1 Aim of the study

This study examines the differences and similarities of the endoscopic and the surgical approach. It will also review the pros and cons of both treatments. The focus hereby lies in quality of treatment and quality of life. It aims to give a practical and complete summary of the treatment possibilities for *ampullomas.*

2.2 Study design

The study was conducted as a retrospective, comparative study. The ethics approval was obtained from the Ethics Committee of the University Hospital Ghent. No personal data of the patients were improperly disclosed and there was no safety concern for the patients in this study. Demographics, clinical presentations and statistical findings were evaluated and then compared between the two groups.

2.2.1 Participants

To be able to participate in this study, the patients had to measure up to the inclusion criteria. These criteria are mentioned below. All patients gave their informed consent.

2.2.2 Inclusion criteria

The participants were diagnosed with an *ampulloma* between 2005-2015 and were all above 18 years old at time of diagnosis. Inclusion criteria were adenomas of the major ampulla with no invasive cancer on biopsy and adenomas with carcinoma in situ. Pathology slides were not reviewed for any of these cases. For the policlinic visit, the patients who are still alive were selected.

2.2.3 Exclusion criteria

In the selection of participants, we excluded the patients with familial adenomatous polyposis because of the differences in surveillance, classification,… with sporadic lesions. (3, 30) All non-adenomatous tumours of the duodenal papilla, including gastrointestinal stromal tumours, neuroendocrine neoplasms, leiomyoma, lipomas and adenomyomas were also excluded.

2.2.4 Recruitment

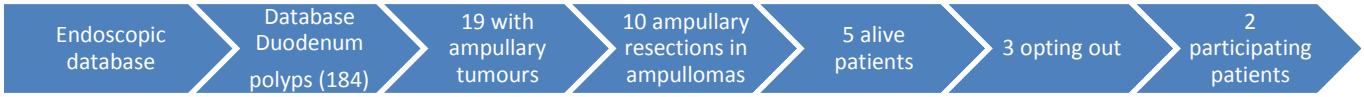
2.2.4.1 Surgery

The department of Hepatobiliary Surgery provided an already existing database. This database contained patients from 2005-2015, who had surgery in the ampullary region. (809 patients in total) After screening on benign *ampullomas*, the total of patients was reduced to

11 patients. Before these 11 patients were contacted, it was carefully checked whether the patients were still alive. After this opting out letters were sent to the patients. The total of participating patients came down to 4 patients.

2.2.4.2 Endoscopy

The Gastro-Enterology department provided their database, that contained all endoscopic patients between 2005-2015 with their nomenclature or their specific classification of their lesions. There, the search terms "ampulloma" and "duodenumpolyp" were used. A database "duodenumpolyps" emerged. (This database contained 184 patients) The database "duodenumpolyp" was screened on features such as "localisation", "benign" and "patients that are still alive".



2.2.4.3 Pathology

Because we had only a few patients, there was decided to contact the department of Pathology. They gave us a database of 334 patients, containing patients with duodenumpolyps. After selection (localisation, benign, alive patients), 8 patients were contacted. After opting out, this number became 6.

The population of living patients sums up to 12 patients, who are willing to participate.

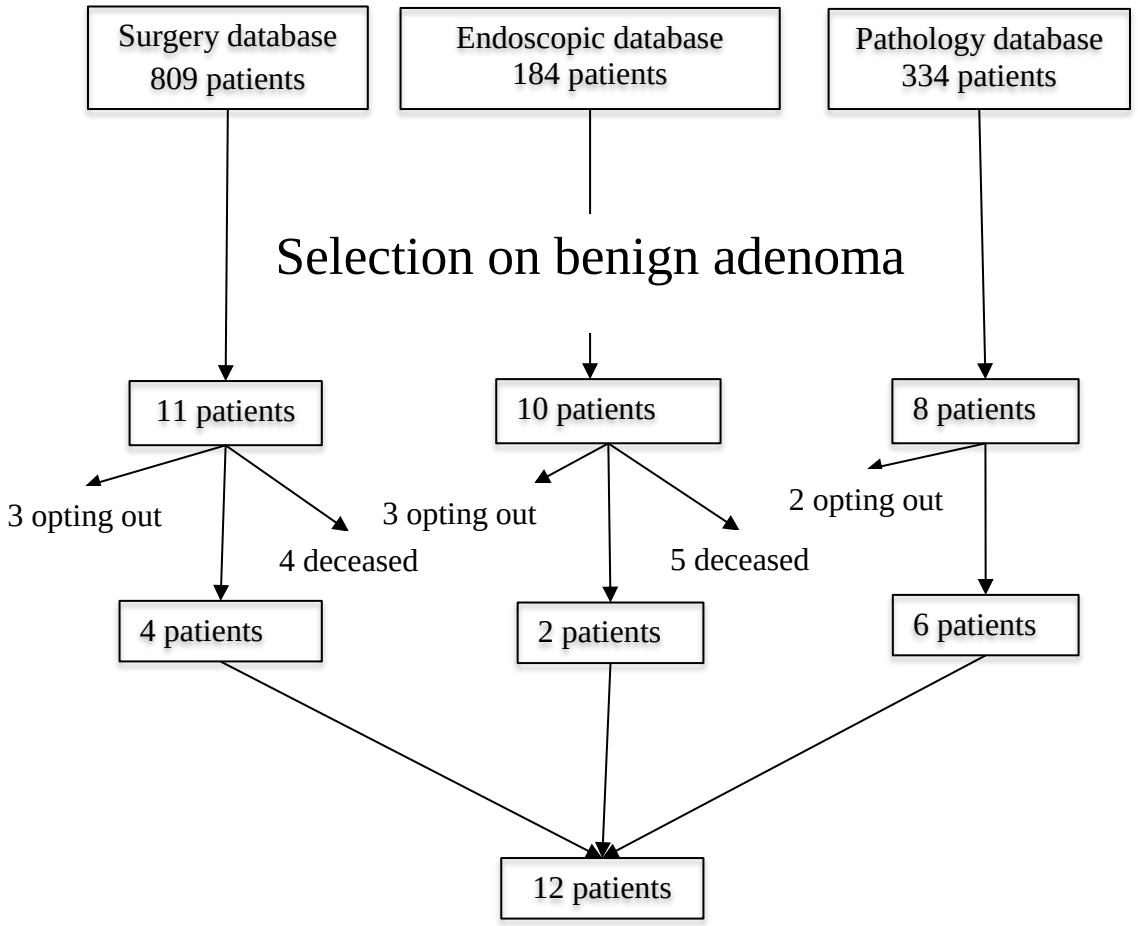


Fig. 14 Algorithm for recruiting the study population

2.3 Questionnaire

To gain data of quality of life of the patients, a questionnaire was set up. This questionnaire (in appendix) consists of two parts. The first part is the SF 12 (the shorted version of the validated SF 36). This questionnaire was used in Dutch for the comfort of the patients. The second part consists of a more specific questionnaire. Since there doesn't really exist a questionnaire for *ampullomas*, there was a questionnaire drafted from several validated questionnaires. (references questionnaire in the appendix) The survey was construed this way so that the problems of conducting only a general or only a specific survey are managed.

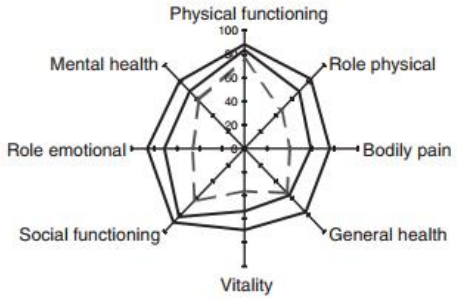


Fig. 15 Conditions tested in the SF 12 (5)

	Generic questionnaires	Disease/treatment specific questionnaires
Comprehensiveness	Comprehensive and wide in scope	Deliberately narrow in scope
Applicability	General applicability over population; low in precision	Targeted to a specific group, conditions or treatment; high in precision
Generalizability	Can be generalized over population and used for comparison, norms or reference values available	Focuses on its target and cannot be used for comparisons between conditions; norms or reference values not applicable
Familiarity	Well known with a widespread use over many years	Unfamiliar, used to a limited extent
Relevancy	Too general for a specific patient population; low in patient and clinician credibility	Highly relevant to its target population; credible to patient and clinician
Responsiveness	Less responsive to treatment induced changes	Highly responsive in detecting small, clinically relevant changes
Practical, logistical and motivational considerations	Lengthy, time-consuming and less acceptable	Short, acceptable

Table 1. Differences in generic questionnaires and specific questionnaires (5)

2.4 Literature

A literature search was performed using the terms " ampulloma ", "endoscopy", "surgery" , "ampullary adenoma", "quality of life", "ampullectomy". Other articles were found by related citations. The articles were selected on title and abstract. To stay relevant, only articles from the last 10 years were withheld. Since the descriptions of the anatomy and the surgical techniques are older, a few older articles were also included.

2.5 Data collection and procedure

The data from the patients was collected through the questionnaires (described in 2.3) and through the EPD (Electronic Patient Dossier).

2.5.1 Questionnaire data collection

The questionnaires were given to and filled out by the patients in a visit to the policlinic or they were sent by post and the patients filled them out at home.

2.5.1.1 Policlinic visit

The patients, who were able and willing to visit, were invited to the policlinic. This visit consisted of a short explanation of the study given by Valentien Merlevede or Karen De Mol. This was followed by filling out the informed consent and the questionnaire itself. The visit was concluded with a short standard clinical examination, which comprised abdominal, respiratory and cardiac tests. Blood pressure was taken and noted.

2.5.1.2 Questionnaire filled out at home

Patients who stated on the phone that they were willing to participate in the study, but couldn't come to the policlinic, were given the option to fill out the questionnaire and informed consent at home. They received their information about the study through the telephone.

2.5.2 Patient information

Extra data were extracted from the EPD (Electronic Patient Dossier). After informed consent, access was granted to the dossiers of the participating patients.

Data extracted from the medical record included patient demographics, clinical presentation, diagnostic findings, treatment, complications. Tumour size and dilated biliary ducts were also pulled from the EPD.

2.6 Statistical analysis

2.6.1 Scoring the SF 12

After obtaining the license for this validated questionnaire, the scoring software of Quality Metric Optum was installed and the data were entered. This way, the scoring happened on a validated manner.

2.6.2 Scoring the specific questionnaire

Although this part of the questionnaire was not validated, we tried to assimilate the scoring system of the SF12. Each item was given a value (e.g. -2 to 2) depending on the number of responses possible, where the worst situation was scored negatively. Then, these scores were multiplied with their weighted factor (important questions got higher weighted factors). Finally, these weighted scores were added and converted to percentages.

2.6.3 Scoring the comorbidity

Since the population consists of elderly people, it was decided to calculate a comorbidity score. The Charlson Comorbidity Index (CCI) was chosen because of its tested validity. The

age-adjusted version was used. (the Charlson Age-Comorbidity Index (CACI)) This version takes the age into account as well as the characteristics **(Table 2)**. (53-55)

CACI	Points
Aids	6
Metastatic solid tumour	6
Moderate or severe liver disease	3
Any non-metastatic solid tumour	2
Malignant lymphoma	2
Leukemia	2
Diabetes with end organ damage	2
Moderate or severe renal disease	2
Hemiplegia	2
Diabetes without end organ damage	1
Mild liver disease	1
Ulcer disease	1
Connective tissue disease	1
Chronic pulmonary disease	1
Dementia	1
Cerebrovascular disease	1
Peripheral vascular disease	1
Congestive heart failure	1
Myocardial infarction	1

Table 2. Scoring criteria for the Charlson Age-adjusted Comorbidity index

2.6.4 Analysis

The analysis of the data was performed with the Statistical Product and Service Solutions (SPSS) version 24.0 software (SPSS Inc., IBM, Armonk, NY, USA). All the continuous data are displayed as mean ± standard deviation and categorical variables are presented in absolute numbers and percentages. The Mann Whitney U and the Fisher exact test were used to test the continuous and categorical variables, respectively. In the statistical analysis, the testing happened two-sided and p-values smaller then 0,05 were considered significant.

III. Results

3.1 Descriptive statistics

Our population consists of twelve patients, who completed a survey. We had five patients, who underwent surgery, five endoscopy and two patients had both treatments. So, all groups are represented and the patients are quite equally divided over the groups (in number and in sex).

3.1.1 Demographics and clinical features

Ampullomas can be found in an elderly population and we see this reflected in these results. The range in this study goes from 53 years up to 78 years. (**Table 3)** According to the Mann-Whitney U test, (for continuous variables in 2 samples; the group endoscopy-surgery wasn't used here since the patients belong in both groups for this variable) this variable wasn't significantly different in the 2 groups. (P = 0.402) This means that the groups don't significantly differ in age. However, the surgical group is averagely speaking younger (mean 61.5 year) than the endoscopy (mean 67 year). This can be explained by the selection criteria for surgery. As surgery requires for people to be in a relative good health. The effect of age on the recovery from surgery or endoscopy will be examined in the discussion.

	N	Mean	Std. Deviation	Range	Median	Q1	Q3
Age (year)	12	65.25	9.687	53-78	65.5	56	76

Table 3. Statistical descriptives for the variable "age"

Mortality was researched, but the reasons for the deaths in this research population was due to other causes than the treatments of the *ampulloma* or it was unknown.

As to the variable 'sex', it can be noted that there were overall more women than men in this study. The percentage in women was equal in both groups. Both had 60% women.

Comorbidity is depicted by the CACI (explained before). There weren't any patients with the CACI level 0, 4, 6, 7, 8. Here, it can be noticed that most patients reached the CACI level 2. **(Table 4)** This is quite good, given the age range of our population. (lower CACI = less comorbidity) It means that the population is quite fit (for their age). The highest CACI was in the group of endoscopy, which is quite logical given that patients have to be fit for surgery and comorbidities have a negative effect on the general health of the patient. So, patients with more morbidity are preferentially treated by the less invasive endoscopy. The difference in

CACI in both groups wasn't significant. (P = 0.554) The group endoscopy-surgery wasn't used here since the patients belong in both criteria for these variable.

Quite remarkable is the fact that the *ampullomas* almost equally gave symptoms as that they were incidentally. (60% was symptomatic in both groups). The clinical features such as "smoker" and "diabetes" were looked up in the EPD, but these data were not found.

		Endoscopy N(column%)	Surgery N(column %)	Endoscopy followed by surgery N(column%)
Sex	Female	3(60)	3(60)	2(100)
	Male	2(40)	2(40)	0(0)
Comorbidity (Charlson Comorbidity Index)	CACI 1	0(0)	1(25)	0(0)
	CACI 2	2(66.7)	2(50)	0(0)
	CACI 3	0(0)	1(25)	1(50)
	CACI 5	1(33.3)	0(0)	1(50)
Clinical presentation	Incidential	2(40)	2(40)	2(100)
	Symptoms	3(60)	3(60)	0(0)

Table 4. Population characteristics and clinical presentation

Only 17% of the whole population filled the survey out at home, which is good since the patients who filled it out in the policlinic could ask for more information about the questions. On the other hand, this type of data collection could lead to an interviewer bias. A definition by BusinessDictionairy: *An interviewer bias is an opinion or prejudice on the part of an interviewer, which is displayed during the interview process and thus affects the outcome of the interview. In research interviews, it is necessary that the interviewer conducts the interview with total objectivity, so that respondents are not influenced by any outside source in their responses*. (56)

		Endoscopy N(column%)	Surgery N(column%)	Endoscopy followed by surgery N(column%)
Filling out survey	Filled out at home	2(40)	0(0)	0(0)
	Policlinic visit	3(60)	5(100)	2(100)

Table 5. Administration survey

3.1.2 Tumour characteristics

As variables for the tumour, the data about diameter of the common duct (Wirsung diameter wasn't found in the EPD) and the size of the lesion were investigated.

The bigger lesions are done by surgery (**Table 6)**. However, there was one big lesion done by endoscopy. The differences between the groups in diameter or size lesion was not significant, due to small sample size and missing data. (6 missings in total: 1 in the endoscopy followed by surgery group, 3 in the endoscopy group and 2 in the surgery group) (P = 0.268) The mean of the sizes in general was 24.2 mm and for the endoscopy 18.6 mm and for the surgery 27.3 mm .

		Endoscopy N(column%)	**Surgery N(column%)**	**Endoscopy followed by surgery N(column%)**
Diameter of the common bile duct (mm)	5 mm	1(100)	0(0)	0(0)
	6 mm	0(0)	0(0)	1(100)
	8 mm	0(0)	2(100)	0(0)
	9 mm	1(50)	1(50)	0(0)
Size of the ampullary lesion (mm)	10-20 mm	4(80)	1(20)	0(0)
	21-30 mm	0(0)	1(100)	0(0)
	31-40 mm	1(25)	2(50)	1(25)

Table 6. Tumour characteristics: percentages per group

3.1.3 Procedure characteristics

Pancreatitis is the most feared complication of endoscopy. (2, 9, 29, 32, 42, 45, 48) To prevent this, a pancreatic stent is placed. Here, we also see pancreatic placement in 80% of the endoscopic treatments. **(Table 7)** (endoscopy + endoscopy followed by surgery) In surgical ampullectomies, it isn't standard to place a pancreatic stent. There, it is more likely to place a biliary catheter. Because of the incomplete reports about placement of the catheter, this variable wasn't included in the database.

In the procedure of a surgical ampullectomy, specimens can be sent for frozen section evaluation. When the edges of the specimen are not free of tumour tissue, a referral to PDE or Whipple has to be done. (51) So, it is logical that none of the endoscopy procedures had a referral to Whipple. In 20% of the surgical ampullectomies, the referral had to be done, with

the vanishing of all the advantages of local ampullectomy as a result. In the endoscopy to surgery group, the only surgical option is Whipple. (after recurrence or incomplete resection, there is only Whipple as therapeutic option)

Incomplete resection was found most in the endoscopy: one patient in the 'pure' endoscopy group and one in the endoscopy to surgery group. The group that went from endoscopy to surgery, had an incomplete resection or recurrence. As to be seen in table 9, one patient had recurrence from the endoscopy-surgery group. So, the other patient had an incomplete resection. This incomplete resection was due to the endoscopy, not the surgery. Both patients of the endoscopy to surgery group filled out the survey after their surgery and no recurrence or incomplete resection was mentioned afterwards. This brings the incomplete resection of endoscopy to 2 (2 out of 6). This is higher than the surgery group. (0 out of 5)

		Endoscopy N(column%)	**Surgery N(column%)**	**Endoscopy followed by surgery N(column%)**
Placement of pancreatic stent	No	1(20)	4(80)	0(0)
	Yes	4(80)	1(20)	2(100)
Referral to Whipple	No	5(100)	4(80)	0(0)
	Yes	0(0)	1(20)	2(100)
Complete resection	No	1(20)	0(0)	1(50)
	Yes	4(80)	5(100)	1(50)

Table 7. Procedure characteristics

3.1.4 Pathologic findings

Low-grade dysplasia was mostly done by endoscopic approach, although there are some *ampullomas* with low-grade dysplasia done by local surgery. **(Table 8)** The moderate and high grade dysplasia *ampullomas* were mostly done by surgery, which is the normal procedure. A real significant difference wasn't found. (P = 0.358) In the endoscopy-surgery group, the APD information is given of *ampulloma*, removed by the surgery.

		Endoscopy N(column%)	**Surgery N(column %)**	**Endoscopy followed by surgery N(column%)**
APD information	Low-grade dysplasia	4(80)	3(60)	0(0)
	Moderate dysplasia	1(20)	1(20)	1(50)
	High-grade dysplasia	0(0)	1(20)	1(50)

Table 8. Pathological findings

3.1.5 Recurrence

Recurrence is the 'de novo' redevelopment of an *ampulloma*, even though the last resection was considered successful. Recurrence was found once in every group. The endoscopy followed by surgery group had 1 incomplete resection and 1 recurrence. This recurrence happened after endoscopy and the choice was then made to do a PDE. So the recurrence count after endoscopy is 2 of 6 patients (33%) and the surgery recurrence is 1 of 5 patients (20%).

		Endoscopy N(column%)	Surgery N(column%)	Endoscopy followed by surgery N(column%)
Recurrence	No	4(80)	4(80)	1(50)
	Yes	1(20)	1(20)	1(50)

Table 9. Recurrence rates

3.1.6 Post-resection morbidity

Most complications were found in the endoscopy group, with pancreatitis as the biggest complication followed by bleeding. Pain was overall present after the procedures. It probably was a little less in the surgery group, since the use of a pain pump is more standard after a surgery. In comparing the endoscopy and surgery group the "endoscopy-surgery" group was put together with the endoscopy group, since the complications mentioned in that group were the complications experienced after the endoscopic treatment. The p-value for the fact of having complications was 0.152 and pancreatitis and pain were 0.106 and 0.925. However, the difference in bleeding was significant. (P = 0.047). Since the sample size is small, a 95% confidence interval has to be calculated. Bleeding occurs in 33% of the entire population. The confidence interval is from 29.8% to 36.2%.

		Endoscopy N(row%)	Surgery N(row%)	Endoscopy followed by surgery N(row%)
Complications	No	0(0)	2(100)	0(0)
	Yes	5(50)	3(30)	2(20)
Bleeding	No	2(25)	5(62.5)	1(12.5)
	Yes	3(75)	0(0)	1(25)
Pancreatitis	No	2(22.2)	5(55.6)	2(22.2)
	Yes	3(100)	0(0)	0(0)
Pain	No	2(28.6)	3(42.9)	2(28.6)
	Yes	3(60)	2(40)	0(0)

Table 10. Complications

3.1.7 Long-term morbidity

Long-term morbidity is defined here by the morbidity that could be related to the procedure. These are mainly gastro-intestinal symptoms. Long-term morbidity was determined by asking about flatulency, bloating, losing weight, vomiting and an upset stomach. (Other symptoms such as nausea, constipation, not much of an appetite were also asked but none of the patients had these symptoms). These symptoms were not significantly different in both groups (the p-values are for flatulency, bloating, losing weight, vomiting, upset stomach are respectively 0.513, 1,0.513,0.317 and 0.221)

		Endoscopy N (% of total)	Surgery N (% of total)	Endoscopy followed by surgery N (% of total)
Flatulent	No	4(33.3)	3(25)	2(16.7)
	Yes	1(8.3)	2(16.7)	0(0)
Bloated	No	4(33.3)	4(33.3)	2(16.7)
	Yes	1(8.3)	1(8.3)	0(0)
Lost weight	No	4(33.3)	3(25.0)	2(16.7)
	Yes	1(8.3)	2(16.7)	0(0)
Vomiting	No	5(41.7)	2(33.3)	1(8.3)
	Yes	0(0)	1(8.3)	1(8.3)
Upset stomach	No	4(33.3)	2(16.7)	2(16.7)
	Yes	1(8.3)	3(25.0)	0(0)

Table 11. Long-term morbidity

3.2 Comparison SF 12 to the specific questionnaire

The SF12 was first compared to the specific questionnaire. The Mann-Whitney U was not significant (P= 0.368) so the hypothesis that there are significant differences between the two questionnaires, can't be accepted. Thereby, it can be concluded that both questionnaire are alike. This test was not conducted as a means to use the SF12 to validate the specific survey. Out of this result, we might cautiously conclude that when a patient would score well in the SF12, he could score well in the specific survey because when a patient is general well, the patient could tolerate more bad things. In appendix, a figure can be found comparing the data from our population to the general population. There, we see that the population almost assimilates the general population.

3.3 Comparison endoscopic approach versus surgical approach

A table of all the responses of whole the population can be found in the appendix. In the next section, some important questions were compared.

3.3.1 SF 12 comparison between the two approaches

General health score: Most patients seem to be in good general health in both approaches (this corresponds with the low morbidity scores). Although in the surgery group, there were 2 patients who scored themselves less than good. This can be explained as follows: surgical ampullectomies give more morbidity than the endoscopic approach. (18% endoscopy vs 42% for surgical ampullectomy. (2, 11, 30, 31, 44)) More comorbidity gives a worse overall health in general.

Limited in moderate activities (moving a table, pushing a vacuum cleaner,...): Here, the surgery group also scores a little less than the endoscopy group. The moderate activities that are mentioned here, contain the use of abdominal wall muscles and in the surgery group, there were some troubles with the abdominal muscles.

Accomplished less than the patient would like as a result of mental health?: We see here that both of the groups score quite good on mental health. So the procedures don't affect the mental health too badly.

Comparison of the total scores of the SF12 between the groups: The differences between the surgical approach and the endoscopic approach were not significant. (P = 0.076) The mean score for the endoscopy group was 0,70 and was 0,71 for the surgical group. So, in general health, there is no difference in the groups.

	N	Mean	Std. Deviation	Range	Q1	Median	Q3
Total score questionnaire SF12	12	0.7124	0.12094	0.47- 0.92	0.6525	0.7230	0.7588

Table 12. Descriptive statistics for the total score of SF12

3.3.2 The specific survey comparison between the two approaches

Are you able to walk 100 meters at brisk pace? This question tries to represent the physical condition. It is noticeable, that the endoscopy group has more troubles with this action compared to the the surgery group. Older people that are not fit for surgery, are more likely to be referred to endoscopy so the patients with a worse physical condition are part of the endoscopy group.

Do you still go out? (family or friends visit, other outdoor activities, etc.): The procedures, as in the SF12, don't have an effect on the social life of the patients.

Do you experience pain in the abdominal region? Pain is most experienced by the surgery group, which deteriorates the quality of life.

Pain region: Most 'pain' was felt in relation to the digestion. This was most seen in the surgery group.

How much of the time do you experience pain in the abdominal region? Most pain and the highest frequency of pain is found in the surgery group, which gives a negative image to the surgery.

Did the pain disturb your sleep? In both groups, the pain isn't inflammatory or so bad that it disturbs the sleep of the patients, which is very good.

How often do you participate in a social activity? Here, the surgical groups scores a little bit worse than the endoscopy group, which shows that surgery may have an effect on the social life of the patients.

Do you have troubles with lifting? As to be expected, in the activities involving the abdominal muscles the surgery groups scores worse than the endoscopy group because in the endoscopy group, the abdominal wall was not penetrated.

Does the cicatrice bother you? With endoscopy, there is no cicatrice of course. However, in the surgical group the cicatrice doesn't bother the patients all that much, so the cicatrice is not so much relevant as a negative aspect of the surgery.

In general, are you satisfied with the result of the procedure? Overall, the patients were satisfied with their procedure, surgery or endoscopy.

How long did it take before you could resume your everyday activities? The responses are quite the same in both groups, although the surgical group was longer inactive than the endoscopy group.

Comparison of the total scores of the specific survey between the groups:

The differences between the surgical approach and the endoscopic approach were not significant. The mean score for the endoscopy group was 0.78 and was 0.60 for the surgical group. So, the quality of life is on average lower in the surgical group, only the difference is not significant. (P= 0.167)

	N	Mean	Std. Deviation	Range	Q1	Median	Q3
Total score specific survey	12	0.7002	0.15151	0.38-0.93	0.5844	0.7291	0.7926

Table 13. Descriptive statistics for the total score of specific questionnaire

IV. Discussion

Endoscopy has been known for its less invasive technique; the patients recover more quickly and there is supposedly less morbidity. (3, 9-11) Even for rare tumours like *ampullomas*, this technique has been researched for many years to replace the more aggressive and invasive surgical approach. (1) The major obstacles for endoscopy to replace surgery are the risk of incomplete resection and the risk of pancreatitis and bleeding. How are these problems managed? Does endoscopy result, despite the obstacles, in a better quality of life?

The main issue in this thesis is the incomplete resection. First off, risk factors associated with incomplete resection as well as factors associated with complete resection are still not clarified, because of incomplete reports in the literature. According to Wiriyaporn *et al*., a lower mean age, no jaundice at time of presentation would give a greater chance to complete resection, but more research is needed here because the skill of the endoscopist wasn't really taken into account. Nowadays, it is mostly stated in the literature that endoscopy has the most incomplete resections. (range from 8-29% for endoscopy) (2, 9, 32, 46) **(see table 14 & 15)** This result is mirrored in this thesis, where EP indeed has the most incomplete resections.(33% vs surgery with 0%)

Another of the problems with managing *ampullomas* is the recurrence. The recurrence rates in studies are displayed in table 14. There, we can see that these rates for endoscopy go from 0-33%, with a mean of 14%. So the rate in this study (33%) concurs with this range. (9, 10, 30) Even the recurrence rate for surgery (20%) lies in the range given by other studies. (0% -25% for ampullectomy). (2, 3, 11, 24, 41) **(see table 15)**. Since the recurrence rates of both procedures lie kind of in the same range, the issue arises whether the extra morbidity caused by SA is compensated by the lower recurrence rates?

In this study, the answer lies in the quality of life, which will be further discussed.

Study	No. of patients	Complete resection, no. (%)	Malignant foci	Recurrence, no. (%)	Surgery
Binmoeller *et al.*	25	23/25 (92)	0/23	6/23 (26)	3/25
Desilets *et al.*	13	12/13 (92)	0/12	0/12(0)	1/13
Catalano *et al.*	103	83/103 (81)	6/83	10/103 (10)	16/103
Cheng *et al.*	55	39/55 (71)	7/39	9/27 (33)	4/55
Kahaleh *et al.*	56	30/56 (54)	21/56	NA	12/56
Bohnacker *et al.*	87	74/87 (85)	NA	15/87 (17)	17/87
Irani *et al.*	102	86/102 (84)	8/102	8/102 (8)	16/102
Kim *et al.*	72	65/72 (90)	3/72	5/65 (8)	2/72
Napoleon *et al.*	79	70/79 (89)	8/79	5/69 (7)	5/79
Ridtitid *et al.*	151	107/151 (71)	12/151	16/107 (15)	NA

Table 14. Outcomes of endoscopic papillectomy in published studies in patients with ampullary adenoma without intraductal invasion (32)

Study	Year	N (Benign: Malignant)	Recurrence %	Mortality %	Morbidity %
Chareton *et al.*	1996	8 (2:6)	NR	0	25
Rattner *et al.*	1996	14 (9:5)	11	0	14
Beger *et al.*	1999	47 (37:10)	0	0	NR
Clary *et al.*	2000	18 (14:4)	0	0	29
Posner *et al.*	2000	21 (18:3)	11	0	62
Heidecke *et al.*	2002	20 (18:2)	11	0	40
Miossee *et al.*	2004	8 (7:1)	0	0	75
Dixon *et al.*	2005	19 (12:7)	25	0	37
Demetriades *et al.*	2005	20 (8:12)	0	0	10
Roggin *et al.*	2005	29 (21:8)	NR	0	31
Ouaïsso *et al.*	2006	26 (20:6)	15	0	8
Gorbmyer *et al.*	2008	29 (25:4)	8	3	45
Tien *et al.*	2009	20 (17:3)	NR	0	10
Winter *et al.*	2010	15 (13:2)	20	0	33
Ceppa *et al.*	2011	41 (34:7)	9	0	42

Table 15. Surgical ampullectomy data (37)

Morbidity is caused by complications post-procedure and it also contains the long-term discomfort. The complication rate post-procedure in this study is of the same level as the literature, even though there are some differences. (probably related to the skill and experience of the endoscopist and due to the small sample size) (44) For example, in this study pancreatitis was seen in 33% of the cases (in literature this number is around 8-30% (2, 9, 29, 32, 42, 45, 48)) **(see table 16)**. This could be explained by the clinical presentation. The majority of the population of this thesis had symptoms of the *ampulloma*. These symptoms are mostly provoked by the ampullary obstruction, which could lead to more inflammation of the structures, such as the pancreas, therefore creating pancreatitis. Pancreatitis is being managed by placing a stent, but it still happens. Bleeding also occurred in this analysis, but was adequately controlled by endoscopic modalities. Still, it was considered as a relevant difference in endoscopic and surgical approach.

Study	No. of patients	Pancreatitis	Bleeding	Perforation	Cholangitis	Stricture	Mortality
Binmoeller *et al.*	25	3/25 (12)	2	0	0	0	0
Desilets *et al.*	13	1/13 (8)	0	0	0	0	0
Catalano *et al.*	103	5/103 (5)	2	0	0	3	0
Cheng *et al*.	55	5/55 (9)	4	1	0	2	0
Kahaleh *et al*.	56	4/56 (7)	2	0	1	0	1
Bohnacker *et al.*	87	11/87 (13)	18	0	0	0	0
Irani *et al.*	102	10/102 (10)	5	2	1	3	0
Kim *et al*.	72	6/72 (8)	12	0	0	0	0

Table 16. Complications of endoscopic papillectomy in published studies in patients with ampullary adenoma without intraductal invasion (32)

In this thesis, not only the post-resection morbidity was researched, but also the morbidity that could be caused by the procedure in the long run. These were expressed by the symptoms (unbearable pain, bleeding, wound infection, leakage, perforation, weight loss, nausea, vomiting, bloating, flatulent, upset stomach, constipation, loss of appetite). The most long-time morbidity was found in the surgery group. Unfortunately, this kind of morbidity wasn't asked in other studies, so there is no comparison possible. Still, it is important to ask about these symptoms in relation to HRQL.

When it comes to comparing HRQL, there wasn't much to be found in the literature. This is probably due to the difficulty of qualitative research. It is a subjective way of researching (the opinions, emotions, expectations of the patients are interviewed), which makes it difficult to come to objective conclusions. Even though the difference wasn't statistically significant (because of the small sample size), quality of life is becoming an important term/research method in these times (as mentioned in 1.5) and it should be investigated further. In this research, the quality of life of the endoscopy patients was higher than the surgery group.

Now, some statements have been made, but we have to keep in mind that this study has many limitations. The small sample size is the biggest deficit hereby. It limits our possibilities to make solid conclusions regarding treatment possibilities of an *ampulloma*. This small sample size is due to the following factors. A few of the patients had already died (other causes than the *ampulloma*) and there were a lot of opting outs. This study was also conducted in a single center with a limited follow-up. Part of the population could also have been missed because of the variety in nomenclature. This brings us to the other weakness, the retrospective design. Because the procedures all happened before the start of the study, the structure of the clinical decision-making wasn't always clear and a lot of data were missing in the EPD files. This could be avoided by a prospective design. Another limitation, but at the same time a strength, is the specific survey. It is true that the questionnaire used is not validated, but the specific questions did give a better view of the quality of life in this specific situation. We used a part of the Gastrointestinal Quality of Life Index (GQLI) (that covers symptoms such as pain, bloating, dysphagia and diarrhea). We didn't use the scores attached to this index because when being summed up with the score of the specific survey, the validation of the GQLI doesn't apply anymore. We did use the SF 12 as validated questionnaire, but there, it has to be considered that this scoring software uses US weighted scores. Fang *et al.* investigated whether the use of UK and Canadian preference weights would lead to the computation of different health utility scores in a sample of persons with Alzheimer's disease and their primary informal caregivers. This is an important investigation because when using a validated survey, the user will unknowingly draw upon the preference weights of other populations, regardless of whether the other populations' weights are transferable. Unless transferability is assessed, researchers can't be certain whether another population's weights will provide unbiased health utility scores in their population of interest. The study suggested that health utility scores can be similar for people across countries with comparable socio-demographic characteristics (i.e., UK, Holland, Germany, Spain,..). It concluded that the US

can be similar to the UK (and the UK can be similar to Holland and Belgium), but that we still have to be careful with the scores. (57)

Another strength of this study is (even though the pre-operative evaluation is difficult and there is no consensus or guidelines) that this study compares the two techniques and it comprises also the aspect of quality of life. There are not a lot of studies comparing surgical and endoscopic treatment for ampullary adenoma and certainly not with the focus on quality of life. This is also the relevance of this research.

As general variables in this study, age and comorbidity were included in the database. Do these factors also concur with the literature? The age range (53 - 78 years), for instance, coincides with what is stated in the literature. (age range from 40 to 87 years) (1, 6, 8, 11, 21, 24, 27, 37). It means that the population in this study, how small it may be, could have a simular make-up as the populations in the literature.

Also for the variable "sex", it kind of follows the literature. Rosenberg *et al*. stated that *ampullomas* are equally divided under the sexes, but it varies among the studies. (between 40-60%) (1, 6, 8, 11, 21, 24, 27, 30, 37) In this study the women are in the majority of the population. Now, sex doesn't have a big effect on the outcomes in this study. (since the groups that are being compared have the same percentage of women)

However, age is an important factor in this research because it has an effect on the recovery after surgery. Many of which have to do with wound healing. A few important factors hereby are mentioned:

- Reduced skin elasticity: When people get older, their skin loses elasticity due to degradation of the elastic tissue and collagen fibers. These components give flexibility and strength to the tissue, but they also help recover and restore the tissue to its original state. When tissue is less elastic and flexible, it is more difficult for the skin to return to its natural shape and color. This means older people have a higher risk of scarring from a wound.
- Slower collagen replacement: Lower levels of collagen can slow down wound healing, because collagen is needed for cellular development and tissue regeneration within all layers of the dermis.
- Age-related diseases: Certain diseases and medical conditions are more common in the elderly than the younger population. Cardiovascular disease, diabetes and others – particularly those that affect blood flow – can be bad for the recovery process. When blood

cannot properly reach the affected area, it becomes malnourished and low in oxygen, thereby stalling the wound healing.

- The older the person, the more difficult healing gets (58)

It can be observed that the patients for surgery are averagely speaking younger than the endoscopy patients. (37) Even in this study, the surgery group was on average younger. (mean 61.5 vs 67 years). This seems logical since there are certain conditions that need to be fulfilled before undergoing surgery. In other words, the patients have to be 'fit'. Although 'fit for surgery' doesn't rely on age alone. Hentati *et al*. and Kala *et al.* stated that age alone shouldn't be a contraindication for surgery. (1) They explained that resection of ampullary tumours is safe in correctly selected patients of advanced age, with morbidity and mortality rates approaching those observed in younger patients. So comorbidity is also an important factor.

As to comorbidities, it is very difficult to compare these comorbidities to the comorbidities mentioned in the literature. Either comorbidities are not mentioned or the term 'comorbidities' is mentioned, but not which comorbidities. Also, the variety of existing comorbidities and the different meanings in QOL of comorbidities make the comparison difficult. In this study, a validated scoring system was used to make the load of the comorbidities apprehensible and maybe usable for comparisons later on. Although caution is needed with using this index score, since there were data missing which could influence these scores.

The clinical presentation in this study is different from the literature. (24) Normally, *ampullomas* are often asymptomatic and incidentally found on endoscopy. In this study, there were more symptomatic *ampullomas* than asymptomatic. This could be due to several factors such as not every *ampulloma* is being noticed or treated, patients with asymptomatic *ampullomas* already died,…

When talking about the diameter of the lesions in this study, the range of the lesions is simular to the range stated in the literature.(10-40 mm in this thesis and 10 mm up until 70 mm in the literature) (3, 5, 22, 26, 27, 29, 33, 38, 49, 51, 59, 60) The size of a lesion is important because, at the moment, it is one of the criteria for the treatment possibilities. However, there is still some vagueness about the indications. There is one absolute indication: an adenoma confined to just the ampullary region (not in Oddi's sphincter), absence of extension into the pancreatic or biliary ducts, no evidence of malignancy, no invasion of the duodenal muscular

layer and with a size less than 4 cm. (2, 10, 25, 32, 33, 36, 42) Other indications are still under investigation. For instance, cancer foci in an adenoma without invasion of the muscularis propria of the duodenum, pancreas or extension along the bile or pancreatic duct are a possible indication for an endoscopic approach, although more data is needed to confirm this. (45) The application of piecemeal resection resulted in a gradual increase in the size of the tumour resected. Even so, many authors recommended that lesions of 4 cm or more should not be treated endoscopically, even though there are reports of successful endoscopic resection of ampullary lesions of greater size. (up to 7cm) (24, 33) In this study, the largest size was 4 cm, but not all small sizes were done endoscopically; smaller sizes were sometimes resected by surgery. The question arises: is size important in choosing the best treatment? The size of the lesion can affect the endoscopic approach to resection according to Chini *et al*. (24, 33) However, Maneghetti *et al*. reported that tumour size did not influence recurrence rate and was not a predictor of the coexistence of malignancy. (24, 33)

As another tumour characteristic, the diameter of the common duct was used. As previously said, Dowdy *et al*. reported that the diameter of the common duct is 1–4 mm, with an average of 2.6 mm. In this study, the average diameter was 6 mm, which is enlarged, but not so that it can be an indicator of cholangitis or pancreatitis. (36) Besides, Rienhoff *et al*. found that the presence and length of a common duct are closely associated with the symptoms of reflux of pancreatic juice into the biliary tract. (19) These lengths of the common duct were not registrated in this study. Besides the tumour size, the tumour is also defined by its pathologic character. In 75% of the cases low or medium grade dysplasia was found, which is similar to other studies. (ranges form 50-80%) (2, 3, 5, 34, 38, 45, 46) It seems understandable that the low-grade dysplasia tumours were done by endoscopy and higher grade dysplasia would be done by surgery, but other studies such as the study of Patel *et al.* prove that also moderate or high grade can be done by endoscopy. (3, 38) This is also true for this investigation. **(Table 8)** However, Kim *et al.* suggested that ampullary adenoma with preprocedural high grade dysplasia or more than 1.5 cm should not be managed with endoscopic papillectomy due to high associated rates of recurrence. (11, 33, 42) Other investigators have advocated endoscopic resection for high grade dysplasia if the tumour is only extraductal, and in situations where intraductal growth is less than 1 cm. For other authors, endoscopic resection is not contraindicated even in the case of evidence of a high-grade dysplasia. (2, 5) Still, caution is needed, since high-grade lesions aren’t always recognized as such in the pre-

procedural stage and high- grade dysplasia also can harbor some elements of focal early cancer. (21, 24)

Aside from using the endoscopy for big lesions, Nguyen *et al*. described another potential use of endoscopy in the elderly. The therapeutic role, either curative or palliative, of EP in elderly patients deserves special attention because: (a) patients who present with ampullary tumours are middle-aged (b) a significant proportion of these patients have co-morbidities that render them surgically unfit; and (c) these patients tend to have a higher rate of morbidity and mortality from radical PDE. Unlike the situation with surgery, age has not been shown to be a discriminating factor for outcomes of therapeutic upper gastrointestinal endoscopy. (as mentioned in the age effect on wound healing in the discussion) The study of Nguyen *et al.* showed that EP resulted in curative resection in all elderly patients with ampullary adenomas. Even in patients with locally invasive ampullary carcinoma, EP provided an effective mode of palliation that resulted in median survival duration of 26 months. Deaths directly related to invasive carcinoma were uncommon (7%), with most deaths due to coexisting illnesses, especially cardiac disease. Thus, endoscopic papillectomy appears to be the treatment of choice in elderly patients, particularly those who are unfit for surgical resection. (44)

This potential of endoscopy use brings us back to the problems with indications and staging of these tumours. As said in 1.1.4 biopsy, EUS, ERCP are used for evaluation of malignancy, but these techniques are not perfect. A classification on endoscopic view could help. In 2006 Uchiyama *et al*. published findings on ampullary polyps that were classified as I, oval-shaped villi; II, pinecone/leaf-shaped villi; or III, irregular/non-structured. The study concluded that there was a perfect correlation (100%) of type II and/or type III surface structures with what the histology reported as adenoma and adenocarcinoma, respectively. There were only a few positive lesions in their study, so the results were not relevant at that time. Another more recent study with a larger number of patients applied the same criteria and they had 80% accuracy for the detection of adenoma. Pittayanon *et al.* opinionated that this classification could be applicable for ampullary and/or duodenal adenoma diagnosis, but this has not been established or validated. (31)

Lastly, in endoscopy is follow-up also important. The follow–up period could be seen as an additional disadvantage because frequent endoscopic examinations are required after the procedure. Furthermore, specimens obtained after piecemeal resection may have inadequate

margins or false negative results, therefore close monitoring for recurrent or remnant tumours is recommended. (40)

Nevertheless, EP can be an effective primary therapy for ampullary adenoma and it is currently already an interesting option in many cases of ampullary adenoma. However, surgical treatment is very well established and there are no prospects of major changes in the coming years. (25) Still, even in well-selected patients, SA can result in suboptimal outcomes and the need for salvage PDE still exists. (28) In contrast, future evolution in the endoscopic area are a reality and new technologies and standardization of techniques for endoscopic removal of ampullary adenoma may ensure more complete removal and minimal complications related to the endoscopic procedure, expanding the indications for EP. As no guidelines are fully accepted regarding the treatment of ampullary adenomas, the management of this condition relies on the decision of the attending physician or medical staff and depends on the complex interaction of different factors, such as the patient's clinical condition and age, tumour characteristics, physician expertise (surgeons, pathologists and endoscopists) and hospital infrastructure. (25)

Our findings, despite the limitations, concur mostly with the literature and state that EP results in a better quality of life, but it still has a lot of complications. However, SA has its own complications and limitations, which makes it difficult to definitely make a choice between the two approaches. It can however be said with certainty that a thorough evaluation of the *ampulloma* clinicopathologic features (such as degree of tumour extension, lymph node invasion,…) is a necessity for an accurate determination of treatment possibility.

For further improvement in the treatment choices and the quality of life after the procedures, we advocate for more studies involving quality of life, recurrence rates, factors associated with this recurrence, complications and incomplete resection rates. Also, a longer the follow-up duration could help with determining the morbidity and longterm outcomes. All the results of such studies could lead to the formation and development of guidelines. These guidelines, lastly, could give a structure and flowchart for making clinical decisions easier.

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VI. Appendix

6.1 Questionnaire

Naam:……	**Geslacht: M/V/X**
Beroep:……	**Leeftijd: ….. jaar**

Vragenlijst: Kwaliteit leven na de ingreep

Deze vragenlijst gaat enkele aspecten na van uw leven sedert de ingreep. Het eerste deel is een algemene vragenlijst. Het tweede gedeelte is een specifiekere vragenlijst.

DEEL 1 : ALGEMENE VRAGENLIJST (SF-12)

Instructies:
Deze vragenlijst gaat over uw standpunten t.a.v. van uw gezondheid. Met behulp van deze gegevens kan worden bijgehouden hoe u zich voelt en hoe goed u in staat bent uw gebruikelijke bezigheden uit te voeren.

Beantwoord elke vraag door één hokje aan te kruisen. Wanneer u twijfelt over de beantwoording van een vraag, kruis dan de best mogelijke optie aan.

1. Hoe zou u over het algemeen uw gezondheid noemen?

Uitstekend	Zeer goed	Goed	Matig	Slecht
☐	☐	☐	☐	☐

2. De volgende vragen gaan over de bezigheden die u misschien doet op een doorsnee dag. Wordt u door uw gezondheid op dit moment beperkt bij deze bezigheden? Zo ja, in welke mate?

BEZIGHEDEN	Ja, ernstig beperkt	Ja, een beetje beperkt	Nee, helemaal niet beperkt
a. Matige inspanning, zoals een tafel verplaatsen, stofzuigen, zwemmen of fietsen.	□	□	□
b. Een paar trappen oplopen	□	□	□

3. Heeft u de afgelopen maanden, een van de volgende problemen bij uw werk of andere dagelijkste bezigheden gehad, ten gevolge van <u>uw lichamelijke gezondheid sedert uw ingreep</u>?

	Altijd	Meestal	Soms	Zelden	Nooit
a. U heeft minder bereikt dan u zou willen	☐	☐	☐	☐	☐
b. U was beperkt in het soort werk of andere bezigheden	☐	☐	☐	☐	☐

4. Heeft u de afgelopen maanden, een van de volgende problemen bij uw werk of andere dagelijkse bezigheden gehad, ten gevolge van uw <u>emotionele toestand sedert uw ingreep</u> (zoals depressief voelen) ?

	Altijd	Meestal	Soms	Zelden	Nooit
a. U heeft minder bereikt dan u zou willen	☐	☐	☐	☐	☐
b. U was beperkt in het soort werk of andere bezigheden	☐	☐	☐	☐	☐

5. In welke mate bent u de afgelopen maanden door <u>pijn</u> gehinderd in uw normale werk? Zowel werk buitenshuis werk als huishoudelijk.

Helemaal niet	Een klein beetje	Nogal	Veel	Heel veel
☐	☐	☐	☐	☐

6. Deze vragen gaan over hoe u zich voelt en hoe het met u ging in de afgelopen maanden.

	Altijd	Meestal	Soms	Zelden	Nooit
a. Voelde u zich rustig en tevreden?	☐	☐	☐	☐	☐
b. Had u veel energie?	☐	☐	☐	☐	☐
c. Voelde u zich somber en neerslachtig?	☐	☐	☐	☐	☐

7. Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen u gedurende de afgelopen maanden gehinderd bij uw activiteiten (zoals vrienden of familie bezoeken etc.)

Altijd	Meestal	Soms	Zelden	Nooit
☐	☐	☐	☐	☐

DEEL 2 : SPECIFIEKE VRAGENLIJST

Algemene kwaliteit van leven

Hoe zou u uw algemene gezondheid scoren tegenover hoe het was vóór de ingreep?

□ Veel beter nu
want……

□ Beetje beter nu
want……

□ Geen verandering

□ Beetje slechter nu
want……

□ Verergerd nu
want……

Hoe zou u uw fysieke conditie scoren tegenover hoe het was vóór de ingreep?

□ Veel beter nu
want……

□ Beetje beter nu
want……

□ Geen verandering

□ Beetje slechter nu
want……

□ Verergerd nu
want……

Andere relevante medische informatie?

……

……

Fysiek en mobiliteit

1. Kruis aan wat voor u van toepassing is	Geen moeite	Minder moeite dan voor de ingreep	Meer moeite dan voor de ingreep	Niet van toepass -ing
a. Kunt u opstaan vanuit een stoel?	☐	☐	☐	☐
b. Kunt u bukken?	☐	☐	☐	☐
c. Kunt u knielen?	☐	☐	☐	☐
d. Kunt u een trap oplopen tot de volgende verdieping van een huis?	☐	☐	☐	☐
e. Kunt u 100 meter lopen met stevige pas?	☐	☐	☐	☐

2. Kleur het bolletje in bij wat voor u van toepassing is.
Heeft u problemen door de ingreep met sporten?

- ○ Nooit
- ○ Nu minder problemen dan voor de ingreep
- ○ Geen verandering in moeite
- ○ Nu meer dan voor de ingreep
- ○ Nu meer dan voor de ingreep (ik sport minder door de ingreep)
- ○ Niet van toepassing

Gaat u nog op stap? (vrienden, familie bezoeken, andere activiteiten buitenshuis,…)

- ○ Nooit
- ○ Nu meer dan voor de ingreep
- ○ Geen verandering
- ○ Nu minder dan voor de ingreep
- ○ Nu minder dan voor de ingreep (het minder buitenkomen is te wijten aan de ingreep)
- ○ Niet van toepassing

Kunt u gebruik maken van het openbaar vervoer?

- Kost geen moeite
- Kost minder moeite dan voor de ingreep
- Kost meer moeite dan voor de ingreep
- Kon ik al niet zonder hulp voor de ingreep
- Niet van toepassing

Pijn

(omcirkel wat voor u van toepassing is)

Heeft u pijn in de buikstreek? JA/ NEE (omcirkel wat van toepassing is)

Zo JA:

- Gaat het vooral om pijn in <u>de buikwand</u> zelf of pijn omwille van een slechte <u>spijsvertering (maagpijn bijvoorbeeld)</u>? ……..

- Heeft deze pijn te maken met de operatie? JA/ NEE

- Hoe vaak heeft u pijn in de buikstreek?

- Nooit
- 1 keer per week of minder
- 2-3 dagen per week
- 4-5 dagen per week
- Elke dag

- Als u buikpijn had, hoe lang duurde deze pijn?

- Een half uur of minder
- 1 uur
- 2-5 uur
- 6-10 uur

- Hoe zou u uw buikpijn omschrijven wanneer de pijn zijn piek bereikt?

- Geen buikpijn
- Lichte buikpijn
- Matige buikpijn
- Hevige buikpijn
- Ondraaglijke buikpijn

- Hoe zou u uw buikpijn omschrijven op andere momenten (niet wanneer de pijn het ergst is)?

- Geen buikpijn
- Lichte buikpijn
- Matige buikpijn
- Hevige buikpijn
- Ondraaglijke buikpijn

- Heeft de pijn uw nachtrust verstoord?

- Nog niet wakker geworden van de pijn
- Al enkele keren ’s nachts wakker geworden van de pijn (minder dan 1 keer per week)
- Al 1 keer deze week ’s nachts wakker geworden van de pijn
- Al 2-4 keer deze week ’s nachts wakker geworden van de pijn
- Al elke nacht wakker geworden van de pijn

Sociaal en hobby

Beoefent u nu een sport?

- Ja
- Ja, met beperkingen
- Nee, maar voor de ingreep ook al niet
- Nee, ik ben gestopt door de ingreep
- Niet van toepassing

Hoe vaak neemt u deel aan sociale activiteiten?

- 1 x per week of meer
- 1 à 2 x per maand
- minder dan 1 x per maand
- nooit
- niet van toepassing

Hoe vaak hindert uw lichamelijke gezondheid u bij uw sociale activiteiten?

- Nooit
- Zelden
- Soms
- Vaak
- Altijd
- Niet van toepassing

Dagelijkse activiteiten

Kruis aan wat voor u van toepassing is	Nooit	Nu minder problemen dan voor de ingreep	Geen verander-ing in moeite met aan-kleden	Nu meer dan voor de ingreep (maar ik kan het nog altijd zelfstandig)	Nu meer dan voor de ingreep (ik heb hulp nodig bij het aankleden)
a. Heeft u problemen met u aan te kleden?	☐	☐	☐	☐	☐
b. Heeft u problemen met douchen of een bad te nemen?	☐	☐	☐	☐	☐
c. Heeft u problemen om het toilet te bereiken en om er gebruik van te maken?	☐	☐	☐	☐	☐
d. Heeft u problemen met andere activiteiten zoals ……	☐	☐	☐	☐	☐

De operatie

Vindt u dat goede uitleg bijdraagt tot een verbeterde revalidatie? JA / NEE
Als u alles opnieuw moest doen, zou u het opnieuw doen? JA / NEE
Beïnvloeden de complicaties uw leven nu nog? JA / NEE
Zo ja, welke complicatie beïnvloedt u nu nog ? ……

Heeft u last van het litteken? (kleur het bolletjes in bij wat voor u van toepassing is)

- Ik vind dat je het litteken bijna niet ziet
- Ik vind dat je het litteken wel ziet, maar het stoort me niet
- Ik vind dat je het litteken ziet en het stoort me wel
- Ik vind dat je het litteken ziet en het stoort me enorm (Ik verberg mijn buik, ik ben me erg bewust van mijn litteken, ik doe dingen niet omwille van het litteken.)

Complicaties

Kleur het bolletjes in bij wat voor u van toepassing is.
Waren er bij u complicaties?

- Neen
- Ja

Zo ja, dewelke? (symptomen die na de operatie er zijn bij gekomen : u had deze vroeger niet)

- Ondraaglijke pijn
- Wondinfectie
- Interne Bloeding
- Lekkage
- Perforatie
- Vermagering
- Misselijk
- Braken
- Opgeblazen gevoel
- Winderig/ veel boeren laten
- Eten blijft op de maag liggen
- Constipatie
- Niet veel kunnen eten
- Last van maag na het eten

Waren er nog andere complicaties bij u? Zo ja, dewelke?

……..

……

Verblijf en ervaring

Bent u over het algemeen tevreden over de ingreep die bij u gedaan werd?

- Ja, zeer tevreden
- Ja, tevreden
- Neutraal
- Neen, niet tevreden
- Nee, helemaal niet tevreden

Hoelang heeft het geduurd vooraleer u uw dagelijkse activiteiten opnieuw kon hernemen?

- Na mijn verblijf in het ziekenhuis kon ik alles onmiddellijk hernemen.
- Na mijn verblijf in het ziekenhuis kon ik na minder dan 3 dagen mijn dagelijkse
- activiteiten hernemen.
- Na mijn verblijf in het ziekenhuis was ik minder dan een week non-actief.
- Na mijn verblijf in het ziekenhuis was ik meer dan een week non-actief.
- Na mijn verblijf in het ziekenhuis was ik meer dan 2 weken non-actief.

Heeft u nog extra opmerkingen?

……

……

……

……

BEDANKT VOOR UW MEDEWERKING

6.2 References questionnaire

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6.3 Permission to use the SF 12

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License Number: QM037284

Licensee Name: Valentien Merlevede & Karen De Mol c/o University of Ghent

Licensee Address: Parklaan 98, Ghent 9000 BE

Approved Purpose: Endoscopic versus surgical resection of ampullomas: quality of life

Study Name: Thesis/Dissertation
Study Type: Non-commercial academic research and/or thesis – Unfunded Student
Data Collection Method: Interview Script and Paper/Pencil

Therapeutic Area: Cancers

Royalty Fee: None, because this License is granted in support of the non-commercial Approved Purpose

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Signature: Michelle White	Signature: [redacted]
Name: Michelle White	Name: VALENTIEN MERLEVEDE
Title: Director of Consulting Science	Title: STUDENT
Date: 03 OCT 2016	Date: 27/09/2016

Filename: University of Ghent – Valentien Merlevede & Karen De Mol

Karen De Mol
(Co-Licensee)

Signature: K De Mol

Name: KAREN DE MOL

Title: STUDENT

Date: 27/09/2016

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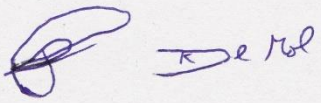

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De Mol

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Valentien Merlevede & Karen De Mol
Parklaan 98
9000 Ghent
Belgium

License Number: QM037284
Amendment to: N/A
Study Term: 09/26/16 to 12/31/16
Master License Term: N/A

Approved Purpose
Endoscopic versus surgical resection of ampullomas: quality of life

Study Name: Thesis/Dissertation
Protocol: Cancers
Govt. ID:
Study Type: STUDENT - FREE
Clients Reference:

Licensed Surveys (Modes) and Services:

Item	Description	Mode of Admin	Quantity	Fees
	OGSR Free Student License Program.			
	SOLUTION PKG: Paper and Interviewer SF12v2			
	with Desktop Scoring Software.			
PROJ01	License Fee		1	
ADMINS	Administrations 20 @ 1 each		100	
ES0170	SF-12v2, Standard Recall	Paper	1	
Approved Languages: Belgium (Dutch)				
IS0170	SF-12v2 Interview Script, Std	Interview Script	1	
Approved Languages: Belgium (Dutch)				
SS100	Scoring Software v5		1	
SS107	SS v5 Key: SF-12v2		100	
EM126	SF-12v2 User's Manual 3rd Ed.		1	
Approved Languages: United States (English)				
	To accept offer, please sign and return			
	license agreement by 20-OCT 2016.			

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Universitair Ziekenhuis Gent

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Afz: Commissie voor Medische Ethiek

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Hepatobiliaire heelkunde
Kliniekgebouw 2-C 2de verdieping
Prof. dr. Frederik BERREVOET
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UW KENMERK	**ONS KENMERK**	**DATUM**	**KOPIE**
	2015/0798	08-aug-15	Zie "CC"

BETREFT Advies voor monocentrische studie met als titel:
Vergelijking van endoscopie vs chirurgie voor ampulloma resecties. (Scriptie Karen De Mol)
Belgisch Registratienummer: B670201525302
Fase (Phase): NVT/NA

* Adviesaanvraagformulier dd. 15/07/2015 (versie 1) (volledig ontvangen dd. 4/08/2015) (versie 1)
* Begeleidende brief dd. 24/06/2015
* CV: Karen De Mol
* (Patiënten)informatie- en toestemmingsformulier
* Informatie- en waarschuwingsnota over de verwerking van informatie voor medisch-wetenschappelijk onderzoek dd. 22/06/2015
  Ondertekend door Karen De Mol
* Informatieformulier:
  - opting out procedure
* Vragenlijsten
  - kwaliteit leven na de ingreep.

Advies werd gevraagd door: Prof. dr. F. BERREVOET ; Hoofdonderzoeker

BOVENVERMELDE DOCUMENTEN WERDEN DOOR HET ETHISCH COMITÉ BEOORDEELD.
ER WERD EEN POSITIEF ADVIES GEGEVEN OVER DIT PROTOCOL OP 8/08/2015. INDIEN DE STUDIE NIET WORDT OPGESTART VOOR 7/08/2016, VERVALT HET ADVIES EN MOET HET PROJECT TERUG INGEDIEND WORDEN.
Vooraleer het onderzoek te starten dient contact te worden genomen met Bimetra Clinics (09/332 05 00).

THE ABOVE MENTIONED DOCUMENTS HAVE BEEN REVIEWED BY THE ETHICS COMMITTEE.
A POSITIVE ADVICE WAS GIVEN FOR THIS PROTOCOL ON 8/08/2015. IN CASE THIS STUDY IS NOT STARTED BY 7/08/2016, THIS ADVICE WILL BE NO LONGER VALID AND THE PROJECT MUST BE RESUBMITTED.
Before initiating the study, please contact Bimetra Clinics (09/332 05 00).

DIT ADVIES WORDT OPGENOMEN IN HET VERSLAG VAN DE VERGADERING VAN HET ETHISCH COMITE VAN 18/08/2015
THIS ADVICE WILL APPEAR IN THE PROCEEDINGS OF THE MEETING OF THE ETHICS COMMITTEE OF 18/08/2015

Muriel Fouquet
Tel: 09/332 33 36
Muriel.fouquet@uzgent.be

Universitair Ziekenhuis Gent
De Pintelaan 185, B-9000 Gent
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- *All members of the Ethics Committee have reviewed this project. (The list of the members is enclosed)*

Namens het Ethisch Comité / On behalf of the Ethics Committee

Prof. dr. D. MATTHYS
Voorzitter / Chairman

CC: De heer T. VERSCHOORE - UZ Gent - Bimetra Clinics
FAGG - Research & Development: Victor Hortaplein 40, postbus 40 1060 Brussel
Prof. dr. R. TROISI

6.5 Figure generated by Quality Metric

Questionnaire QOL ampulloma treatment - SF Comparison for Total Sample

Report Type: SF Comparison for Total Sample

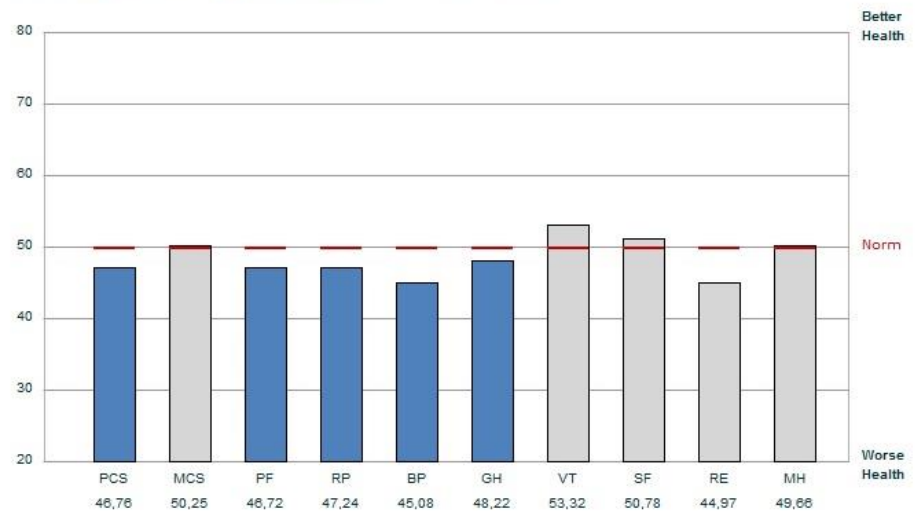
Survey: SF-12v2® Health Survey

QualityMetric

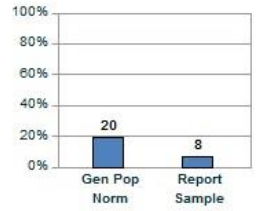
Report Criteria	Demographic Profile	Comments
	Sample Size 12	

Print this report Instructional Guide

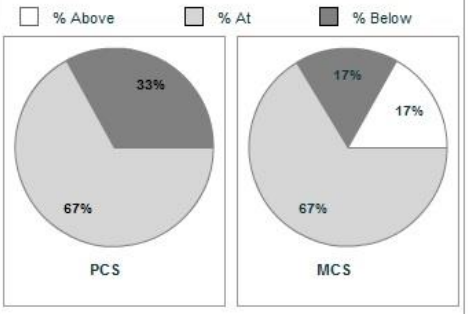
Scores for Total Sample



First Stage Positive Depression Screening: % at Risk



% Sample whose Scores are Above, At or Below the General Population Norm



Note: Totals may not equal 100%, due to statistical rounding.

Abbreviation

PCS = Physical Component Summary
MCS = Mental Component Summary
PF = Physical Functioning
RP = Role Physical
GH = General Health
BP = Bodily Pain
VT = Vitality
SF = Social Functioning
RE = Role Emotional
MH = Mental Health

Note: This report utilizes normative data from the QualityMetric 2009 General Population Sample.

6.6 Statistical tables

6.6.1 Population responses for the SF 12

Questions asked		Endoscopy N(%)	Surgery N(%)	Endoscopy followed by surgery N(%)
General health score	Poor	0(0)	1(100)	0(0)
	Fair	0(0)	1(100)	0(0)
	Good	4(66.7)	2(33.3)	0(0)
	Very good	1(25)	1(25)	2(50)
	Excellent	0(0)	0(0)	0(0)
Limited in moderate activities (moving a table, pushing a vacuum cleaner,...)	Yes, limited a lot	0(0)	2(100)	0(0)
	Yes, limited a little	3(75)	1(25)	0(0)
	Not limited at all	2(33.3)	2(33.3)	2(33.3)
Limited in climbing several flights or stairs	Yes, limited a lot	1(50)	1(50)	0(0)
	Yes, limited a little	3(75)	1(25)	0(0)
	Not limited at all	1(16.7)	3(50)	2(33.3)
Accomplished less than the patient would like to as a result of physical health?	All of the time	0(0)	0(0)	0(0)
	Most of the time	0(0)	1(100)	0(0)
	Some of the time	0(0)	1(100)	0(0)
	A little of the time	4(50)	2(25)	2(25)
	None of the time	1(50)	1(50)	0(0)
Limited in the kind of work or other activities as a result of physical health?	All of the time	0(0)	0(0)	0(0)
	Most of the time	0(0)	2(100)	0(0)
	Some of the time	1(100)	0(0)	0(0)
	A little of the time	3(42.9)	2(28.6)	2(28.6)
	None of the time	1(50)	1(50)	0(0)
Accomplished less than the patient would like as a result of mental health?	All of the time	0(0)	0(0)	0(0)
	Most of the time	0(0)	1(100)	0(0)
	Some of the time	0(0)	0(0)	0(0)
	A little of the time	4(44.4)	3(33.3)	2(22.2)
	None of the time	1(50)	1(50)	0(0)
Limited in the kind of work or other activities as a result of mental health?	All of the time	0(0)	0(0)	0(0)
	Most of the time	0(0)	1(100)	0(0)
	Some of the time	0(0)	0(0)	0(0)
	A little of the time	4(44.4)	3(33.3)	2(22.2)
	None of the time	1(50)	1(50)	0(0)
How much did pain interfere with your normal work in the last months?	Extremely	0(0)	0(0)	0(0)
	Quite a bit	1(50)	1(50)	0(0)
	Moderately	0(0)	1(50)	1(50)
	A little bit	3(60)	1(20)	1(20)
	Not at all	1(33.3)	2(66.7)	0(0)
Have you felt calm and peaceful in the past months?	None of the time	0(0)	1(100)	0(0)
	A little of the time	0(0)	1(100)	0(0)
	Some of the time	0(0)	0(0)	0(0)
	Most of the time	4(57.1)	1(14.3)	2(28.6)
	All of the time	1(33.3)	2(66.7)	0(0)
Did you have a lot of energy	None of the time	0(0)	0(0)	0(0)

in the past months?	A little of the time	1(33.3)	2(66.7)	0(0)
	Some of the time	1(50)	0(0)	1(50)
	Most of the time	3(50)	2(33.3)	1(16.7)
	All of the time	0(0)	1(100)	0(0)
Have you felt downhearted and blue in the past months?	All of the time	0(0)	0(0)	0(0)
	Most of the time	0(0)	1(100)	0(0)
	Some of the time	2(66.7)	1(33.3)	0(0)
	A little of the time	2(33.3)	2(33.3)	2(33.3)
	None of the time	1(50)	1(50)	0(0)
How much of the time has your physical or mental health interfered with your social activities? (like visiting friends, relatives, etc.)	All of the time	0(0)	0(0)	0(0)
	Most of the time	0(0)	1(100)	0(0)
	Some of the time	1(100)	0(0)	0(0)
	A little of the time	1(100)	0(0)	0(0)
	None of the time	3(33.3)	4(44.4)	2(22.2)

6.6.2 Population responses to the specific survey

Questions asked		Endoscopy N(%)	Surgery N(%)	Endoscopy followed by surgery N(%)
General score compared to the time before procedure	Much worse	0(0)	1(100)	0(0)
	A little worse	1(33.3)	2(66.7)	0(0)
	No change	1(25)	1(25)	2(50)
	Much better	0(0)	1(100)	0(0)
	A little better	3(100)	0(0)	0(0)
Physical health compared to the time before procedure	Much worse	0(0)	1(100)	0(0)
	A little worse	2(66.7)	1(33.3)	0(0)
	No change	2(33.3)	2(33.3)	2(33.3)
	Much better	0(0)	1(100)	0(0)
	A little better	1(100)	0(0)	0(0)
Are you able to stand up from a chair?	More effort needed than before procedure	0(0)	1(100)	0(0)
	No effort	5(45.5)	4(36.4)	2(18.2)
	Less effort needed than before procedure	0(0)	0(0)	0(0)
Are you able to bend over?	More effort needed than before procedure	2(66.7)	1(33.3)	0(0)
	No effort	3(33.3)	4(44.4)	2(22.2)
	Less effort needed than before procedure	0(0)	0(0)	0(0)
Are you able to kneel?	More effort needed than before procedure	1(50)	1(50)	0(0)
	No effort	4(40)	4(40)	2(20)
	Less effort needed than before procedure	0(0)	0(0)	0(0)
Are you able to climb one flight or stairs?	More effort needed than before procedure	2(66.7)	1(33.3)	0(0)
	No effort	3(33.3)	4(44.4)	2(22.2)
	Less effort needed than before procedure	0(0)	0(0)	0(0)
Are you able to walk 100 meters at brisk pace?	More effort needed than before procedure	4(80)	0(0)	1(20)
	No effort	1(16.7)	5(83.3)	0(0)
	Less effort needed than before procedure	0(0)	0(0)	0(0)
Do you have troubles with exercising due to the	More than before procedure and because of procedure	0(0)	0(0)	0(0)

procedure?	More trouble than before the procedure	0(0)	1(100)	0(0)
	No change	0(0)	0(0)	0(0)
	Less trouble than before the procedure	0(0)	0(0)	0(0)
	Never	2(100)	0(0)	0(0)
Do you still go out? (family or friends visit, other outdoor activities, etc.)	Never	0(0)	0(0)	0(0)
	Less than before procedure (because of procedure)	0(0)	0(0)	0(0)
	Less than before procedure	0(0)	0(0)	0(0)
	No change	5(50)	3(30)	2(20)
	More than before procedure	0(0)	1(100)	0(0)
Are you able to use public transportation?	I couldn't, even before procedure	0(0)	0(0)	0(0)
	More effort needed than before procedure	0(0)	1(100)	0(0)
	No change in effort	5(50)	4(40)	1(10)
	Less effort needed than before procedure	0(0)	0(0)	0(0)
Do you experience pain in the abdominal region?	Yes	2(28.6)	4(57.1)	1(14.3)
	No	3(60)	1(20	1(20)
Pain region	Abdominal wall pain and digestion problems	0(0)	0(0)	0(
	Digestion problems	1(33.3)	2(66.7)	0(0)
	Abdominal wall	1(33.3)	1(33.3)	1(33.3)
	No pain	0(0)	0(0)	0(0)
Is this pain related to the procedure?	Yes	2(28.6)	4(57.1)	1(14.3)
	No	3(60)	1(20)	1(20)
How much of the time do you experience pain in the abdominal region?	Everyday	0(0)	3(100)	0(0)
	Pain on 4-5 days a week	0(0)	0(0)	1(100)
	Pain on 2-3 days a week	2(100)	0(0)	0(0)
	Once a week or less	1(50)	1(50)	0(0)
	Never	2(50)	1(25)	1(25)
How long does the pain last?	6-10 hours	0(0)	3(100)	0(0)
	2-5 hours	0(0)	0(0)	0(0)
	1 hour	1(100)	0(0)	0(0)
	Half hour or less	4(50)	2(25)	2(25)
	No abdominal pain	0(0)	0(0)	0(0)
How would you describe the abdominal pain when it is at its worst?	Unbearable abdominal pain	1(50)	1(50)	0(0)
	Intense abdominal pain	0(0)	1(100)	0(0)
	Moderate abdominal pain	1(50)	0(0)	1(50)
	Slightly abdominal pain	0(0)	2(100)	0(0)
	No abdominal pain	3(60)	1(20)	1(20)

How would you describe the abdominal pain at a different time?	Unbearable abdominal pain	0(0)	0(0)	0(0)
	Intense abdominal pain	0(0)	0(0)	0(0)
	Moderate abdominal pain	0(0)	1(100)	0(0)
	Slightly abdominal pain	0(0)	2(100)	0(0)
	No abdominal pain	5(55.6)	2(22.2)	2(22.2)
Did the pain disturb your sleep?	Pain has disturbed my sleep every night	0(0)	0(0)	0(0)
	Pain has disturbed my sleep 2-4 times a week	0(0)	1(100)	0(0)
	Pain has disturbed my sleep once a week	0(0)	0(0)	0(0)
	Pain has disturbed my sleep (less than once a week)	0(0)	0(0)	0(0)
	Pain hasn't disturbed my sleep	5(45.5)	4(36.4)	2(18.2)
Are you currently practicing a sport?	Had to stop because of procedure	0(0)	0(0)	0(0)
	No, but also no before procedure	2(33.3)	2(33.3)	2(33.3)
	Yes, with limitations	0(0)	1(100)	0(0)
	Yes	3(60)	2(40)	0(0)
How often do you participate in a social activity?	Never	0(0)	1(100)	0(0)
	Less than once a month	0(0)	0(0)	0(0)
	Once or twice / month	0(0)	1(100)	0(0)
	Once a week or more	5(50)	3(30)	2(20)
How much of the time does your physical health interfered with your social activities	Always	0(0)	0(0)	0(0)
	Often	0(0)	0(0)	0(0)
	Sometimes	0(0)	2(100)	0(0)
	Seldom	1(50)	1(50)	0(0)
	Never	4(50)	2(25)	2(25)
Do you have troubles dressing yourself?	More then before (dependent)	0(0)	0(0)	0(0)
	More then before (independent)	0(0)	0(0)	0(0)
	No change	1(33.3)	1(33.3)	1(33.3)
	Less	0(0)	0(0)	0(0)
	Never	4(44.4)	4(44.4)	1(11.1)
Do you have troubles taking a shower or bathing?	More then before (dependent)	0(0)	0(0)	0(0)
	More then before (independent)	0(0)	0(0)	0(0)
	No change	0(0)	1(50)	1(50)
	Less	0(0)	0(0)	0(0)
	Never	5(50)	4(40)	1(10)
Do you have troubles reaching and using the	More then before (dependent)	0(0)	0(0)	0(0)
	More then before	0(0)	0(0)	0(0)

toilet?	(independent)			
	No change	0(0)	1(50)	1(50)
	Less	0(0)	0(0)	0(0)
	Never	5(50)	4(40)	1(10)
Do you have troubles with lifting?	More then before (dependent)	0(0)	0(0)	0(0)
	More then before (independent)	1(16.7)	4(66.7)	1(16.7)
	No change	1(50)	0(0)	1(50)
	Less	0(0)	0(0)	0(0)
	Never	3(75)	1(25)	0(0)
Do you consider a good explanation of the procedure contributes to a better revalidation	No	0(0)	1(100)	0(0)
	Yes	5(45.5)	4(36.4)	2(18.2)
Would you do it over if necessary?	No	1(33.3)	2(66.7)	0(0)
	Yes	4(44.4)	3(33.3)	2(22.2)
Do the complications still affect your everyday life?	Yes	2(28.6)	4(57.1)	1(14.3)
	No	3(60)	1(20)	1(20)
Does the cicatrice bother you?	Visible and it really bothers me (I cover my stomach because of it)	0(0)	0(0)	0(0)
	Visible and it bothers me	0(0)	0(0)	0(0)
	Visible, but doesn't bother me	0(0)	2(100)	0(0)
	Almost not visible	0(0)	3(60)	2(40)
	Endoscopy	5(100)	0(0)	0(0)
Were there complications after the procedure?	Yes	4(44.4)	3(33.3)	2(22.2)
	No	1(33.3)	2(66.7)	0(0)
In general, are you satisfied with the result of the procedure?	No, not satisfied at all	1(50)	1(50)	0(0)
	No, not satisfied	0(0)	0(0)	0(0)
	Neutral	0(0)	0(0)	0(0)
	Satisfied	1(25)	2(50)	1(25)
	Yes, very satisfied	3(50)	2(33.3)	1(16.7)
How long did it take before you could resume your everyday activities?	After my stay in the hospital, I was non-active for two weeks or more	3(37.5)	4(50)	1(12.5)
	After my stay in the hospital, I was non-active for more than a week	0(0)	1(100)	0(0)
	After my stay in the hospital, I was non-active for less than a week	1(50)	0(0)	1(50)
	After my stay in the hospital, I could resume my activities in	1(100)	0(0)	0(0)

	less than 3 days			
	After my stay in the hospital, I could resume my activities directly	0(0)	0(0)	0(0)