Diplomarbeit

CHANGES OF THE GALLBLADDER IN PATIENTS WITH PANCREATIC CANCER

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Graz, Oktober 2013 *Urša Mali*

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Abstract

Introduction: So far, little attention has been paid to simultaneous inflammatory gallbladder changes and pancreatic cancer and their interdependence.

Methods: We used pre- and post-operative data of 195 patients who were operated for pancreatic cancer in the period from November 2000 to May 2010. The occurrence of cholecystitis and parameters of cholestasis and inflammation were determined and their interdependence with pancreatic cancer was analysed.

Results: Cholecystitis in patients with pancreatic carcinoma was found in 78%. Most of our patients (66.5%) developed cholecystitis due to tumour localisation in the pancreatic head and obstruction of bile drainage, while common risk factors of pancreatic cancer and cholecystitis (e.g. adiposity, diabetes) may be the reasons in others. Analysis of cholestasis and inflammation parameters in combination with possible presence of cholecystitis showed that in patients with cholecystitis and elevated cholestasis and inflammation parameters, cholecystitis is usually due to tumours in the pancreatic head. Risk factors shared by cholecystitis and pancreatic cancer may be reasons for cholecystitis, elevated inflammation parameters and normal cholestasis parameters, while elevated parameters in absence of cholecystitis may occur due to cholangitis. Elevated inflammation parameters without cholestasis or cholecystitis may be attributed to other infections, favoured by a weakened immune system and/or underlying risk factors of pancreatic cancer.

Conclusion: Cholecystitis occurs frequently in patients with pancreatic cancer. Although cholecystitis, elevated cholestasis and inflammation parameters are usually late symptoms of pancreatic cancer and no specific tools for its early detection, they may be important for its diagnosis.

Key words: pancreas; pancreatic cancer; gallbladder; chronic cholecystitis

Zusammenfassung

Einleitung: In der wissenschaftlichen Literatur wird kaum auf den Zusammenhang von entzündlichen Gallenblasenveränderungen und Pankreaskarzinomen eingegangen.

Methodik: Es wurden prä- und postoperative Daten von 195 PatientInnen, bei denen in der Zeit von November 2000 bis Mai 2010 ein Pankreaskarzinom operiert wurde, näher untersucht. Das Auftreten von Cholezystitis und die Cholestase- und Entzündungsparameter wurden erhoben und ihre Beziehung zum Pankreaskarzinom analysiert.

Ergebnisse: Unsere retrospektive Analyse ergab bei 78% der PatientInnen mit Pankreaskarzinom eine Cholezystitis. Bei 66.5% entstand die Cholezystitis aufgrund der Lokalisation des Tumors im Pankreaskopf mit extrahepatischer Obstruktion des Galleabflusses. Bei anderen PatientInnen kann sie aufgrund der gemeinsamen Risikofaktoren von Pankreaskarzinom und Cholezystitis (z.B. Adipositas, Diabetes) aufgetreten sein. Die Analyse von Cholestase- und Entzündungsparametern in Kombination mit möglicher Cholezystitis zeigte, dass die Cholezystitis bei PatientInnen mit erhöhten Cholestase- sowie Entzündungsparametern meistens durch Tumorlokalisation im Pankreaskopf mit Obstruktion des Galleabflusses bedingt ist. Bei den PatientInnen mit Cholezystitis, erhöhten Entzündungs- und normalen Cholestaseparametern können gemeinsame Risikofaktoren für Pankreaskarzinom und für Cholezystitis eine Rolle spielen. Erhöhte Cholestase- und Entzündungsparameter in Abwesenheit von Cholezystitis können durch Cholangitis verursacht sein, während erhöhte Entzündungs- mit normalen Cholestaseparametern und ohne Cholezystitis andere Infektionen als Ursache haben können, die durch ein geschwächtes Immunsystem und/oder zugrunde liegende Risikofaktoren des Pankreaskarzinoms begünstigt werden.

Schlussfolgerung: Cholezystitis tritt bei PatientInnen mit Pankreaskarzinom sehr häufig auf. Obwohl die Cholezystitis, sowie erhöhte Cholestase- und Entzündungsparameter beim Pankreaskarzinom meist Spätsymptome und keine spezifischen Hilfsmittel für Früherkennung sind, können sie wichtige zur Diagnose führende Hinweise sein.

Stichwörter: Pankreas; Pankreaskarzinom; Gallenblase; chronische Cholezystitis

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Abbreviations

ALP	alkaline phosphatase
ATP	Adenosine-5'-triphosphate
BMI	body mass index
CA19-9	carbohydrate antigen 19-9
CD-system	Cluster of Differentiation System
CEA	carcinoembryonic antigen
cm	centimetres
CRP	C-reactive protein
CT	computer tomography
ERCP	endoscopic retrograde cholangiopancreatography
GGT	gamma-glutamyltransferase
LAP	leucine arylamidase
MRCP	magnetic resonance cholangiopancreatography
TNM	The TNM Classification of Malignant Tumours

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1 Introduction

1.1 Pancreas

1.1.1 Anatomy, Histology, Physiology

1.1.1.1 Anatomy

The pancreas is a lightly S-shaped glandular organ between 13 and 18 cm in length that lies in the epigastrium and left hypochondrium and tapers on the rear abdominal wall. It is a part of the digestive and endocrine system and has both endocrine and exocrine functions. The pancreas consists of five sections: head, uncinate process, neck, body and tail.

The head is the thickest and broadest part of the pancreas and lies within the concavity of the duodenum, to the right of the midline. The upper part lies adjacent to the superior part of the duodenum and close to the pylorus. The head border is slightly concave and flattened. The lower part of the head lies close to the inferior part of the duodenum and continues with the uncinate process towards the midline, posterior to the superior mesenteric vessels. It has two surfaces, anterior and posterior. The anterior surface is covered in peritoneum and is associated to the origin of the transverse mesocolon. The posterior surface is almost completely covered by the inferior vena cava, which ascends behind the pancreatic head. The rest of it is related to the right renal vein and the right crus of the diaphragm.

The neck connects the head to the body and is only around 2 cm wide. It is the most anterior part of the pancreas. More precisely, it lies anterior to the superior mesenteric vein and the portal vein and adjacent to the pylorus.

The body of the pancreas lies behind the stomach, on the height of the lumbar vertebrae I-II and is the largest part of the gland. The body is gradually thinning towards the tail. The backside is intergrown to the posterior abdominal wall, but is free of peritoneum and lies in front of the aorta. The front of the body of the pancreas is covered with peritoneum and forms the posterior wall of the lesser sac (omental bursa).

The tail is the narrowest part of the pancreatic gland. It lies between the layers of the splenorenal ligament and can reach up to the hilum of the spleen, anterior to the left kidney. [1–3]

1.1.1.1.1 Vascular supply

The pancreas is rich in arterial supply from two main arteries, celiac trunk and superior mesenteric artery. The head and partly the body are supplied with arterial blood by the superior and inferior pancreaticoduodenal arteries. The superior one originates from the gastroduodenal artery and the inferior one directly from the superior mesenteric artery. Both of these two arteries split into anterior and posterior vessels, which form anastomoses with one another, allowing blood to perfuse the pancreas through multiple channels. Besides the pancreas also the duodenum receives blood from these arteries. There are many branches deriving from the splenic artery supplying arterial blood to the pancreas. The largest two are the dorsal pancreatic artery and the greater pancreatic artery. At the lower border of the pancreas these branches unite to the inferior pancreatic artery, which supplies blood to body and tail of the pancreas.
The venous blood from the body and the tail of the pancreas travels from small pancreatic veins to the splenic vein right into the portal vein. The venous blood from the head of the pancreas flows from pancreaticoduodenal veins to the superior mesenteric vein and, like the splenic vein, lands in the portal vein. [1–3]

1.1.1.1.2 Lymphatic drainage

Lymph of the head of the pancreas is drained via the superior and inferior pancreaticoduodenal lymph nodes to the hepatic lymph nodes and further to superior mesenteric lymph nodes. The lymphatic drainage of the body and tail of the pancreas flows from the superior and inferior pancreatic lymph nodes to celiac lymph nodes, the first one along the splenic artery and the second one along the inferior pancreatic artery. [1–3]

1.1.1.1.3 Innervation

The pancreas is innervated by the autonomic nervous system, like other abdominal organs. Innervation of the pancreas is needed for the regulation of the secretion of the insulin. The fibers of the sympathetic nerves, which suppress the insulin production, come from the celiac ganglia, while the parasympathetic nervous system originates from the posterior vagal trunk, or more precisely, from the coeliac branches of vagus nerve. The parasymphathetic nerves stimulate the secretion of insulin via the neurotransmitter acetylcholine.
The pain fibers accompany the sympathetic supply. Pancreatic pain radiates to the thoracic dermatomes T6 – T10. [1,2,4]

1.1.1.2 Histology

The pancreas is both an exocrine and an endocrine gland.
The exocrine component is purely serous and represents the main part of the gland. It secretes pancreatic alkaline fluid loaded with digestive enzymes, which are involved in the absorption of nutrients and the digestion of carbohydrates, lipids and proteins in the small intestine.
The cells with endocrine function take part in glucose homeostasis and also partly control motility and function of the upper gastrointestinal system. [2,5]

1.1.1.2.1 Exocrine component

The exocrine pancreas has a thin fibrous capsule on its surface and connective tissue divides it into many thousands of lobules, including blood and lymph vessels, as well as nerves. The lobules contain ducts with their end sections. The end sections are arranged in berry-shaped clusters called acini and these are the secretion producers. Acini cells are of pyramidal shape, with wide basis and centrally orientated apexes, surrounding the duct, into which the secretion drains. Like in most of the serous gland cells, also here the round nucleus lies basally, surrounded by unfolded rough endoplasmic reticulum. Middle and apical compartment are filled with thick secretory granules. Three to five acini build an

acini complex, which is connected to the same contact element. From here the secretion drains into intralobular ducts with the cuboidal inner layer, and later into interlobular ducts with the simple columnar epithelium that is active in secretion. Eventually, all the secretion reaches the small and great pancreatic ducts. [2,5]

1.1.1.2.2 Endocrine component

The endocrine portion of the pancreas consists of several hundred thousand bright, differently sized clusters, the islets of Langerhans, which are scattered throughout the darker coloured exocrine glands shares, but are densest in the tail of the pancreas.
Each islet consists of reticularly organised glandular epithelium densely interspersed with capillary vessels. With appropriate histological staining it is possible to differentiate the hormone storage granules and therefore different types of endocrine cells in the electron microscope. [2,5]

1.1.1.3 Physiology

The pancreas houses two morphologically and functionally different tissues. The major part of the pancreas is exocrine serous gland tissue that produces 1.5-2 litres alkaline, enzyme-containing secretion. This flows into the lumen of the acini and then accumulates in intralobular ducts. From here it drains to the main pancreatic duct, which drains directly into the duodenum.
Among the islets of Langerhans, tissue with endocrine function, is completely surrounded by exocrine tissue. In the islets of Langerhans at least five different types of cells produce a range of different hormones that are secreted directly into the blood flow through the capillaries of the exocrine tissue. Glucagon is produced in alpha cells, insulin and amylin (blood sugar regulators) in beta cells, somatostatin (growth hormone-inhibiting hormone) in delta cells, pancreatic polypeptide in gamma cells, and ghrelin in epsilon cells. [4]

1.1.2 Cancerous changes

Changes in the pancreas can be benign or malignant. The benign changes are diagnosed more frequently now than in the past due to more common use of imaging techniques and normally do not need a therapy. They are likely to occur in form of either papilloma (epithelial finger-like growth), solid adenoma or may have a cystic growth pattern.
The most common type of malignant neoplasms in the pancreas is adenocarcinoma, which arises from epithelial exocrine cells. A minority of malignant pancreatic tumours is represented by neuroendocrine tumours, which arise from islet cells. [6]

1.1.2.1 Pancreatic cancer

It is thought that pancreatic malignancies arise from progressive tissue changes, [4] although the aetiology remains unidentified. However, it is known that demographic variables are among the favouring risk factors encouraging the emergence of pancreatic diseases, also known as "the 5 Fs": **f**emale sex, age over **f**orty, **f**ertile, **f**amily history and obesity (**f**at). Other risk factors for tumour formation include: diabetes, chronic pancreatitis and some medications, presumably also alcohol consumption and nicotine abuse. [7,8]
More than half of all the malignancies are localized in the head of the pancreas, 30% in the body or in the tail and around 20% are of multilocular origin. [4,6]

1.1.2.1.1 Ductal adenocarcinoma

The most common type of malignant pancreatic tumours (almost 90% of cases) is ductal adenocarcinoma.
It arises from precursor lesions in the aisles with progressive genetic changes in the oncogene *K-ras* and tumour suppressor genes *p16*, *p53* and *DPC4/Smad4*.
Macroscopically, this type is of white colour and firm consistency. In both, primary tumour and metastases it shows central necrosis and perifocal new tissue formations. This aggravates the already unclear tumour margins. Because the tumour develops in the head of the pancreas in most cases, it usually leads to obstruction of pancreatic ducts in and also outside the gland, and therefore to dilatation of those.

Already in early stages, the tumour grows along the nerves in the dorsal peripancreatic fat tissue. It surrounds the superior mesenteric artery and vein and breaks into the vessels, making the tumour unresectable. The ductal adenocarcinoma also spreads very early to the regional lymph nodes and to the liver.
On microscopic examination, this epithelial tumour has various degrees of tissue differentiation and forms vein-like glands with mucus production. [4,6]

1.1.2.2 TNM classification of Malignant Tumours

The TNM classification is a cancer staging system that describes the extent of tumour in the primary origin, regional lymph nodes and distant locations of the body. [9] Pierre Denoix first devised it in the 1950s. Today, the International Union Against Cancer (UICC) is developing it with the goal of global recognized standards in classification of spread of cancers.

The "T" is used to describe size of the primary tumour and its invasion in the surrounding tissue.

TX: The primary tumour cannot be evaluated.
T0: No evidence of cancer
Tis: Carcinoma in situ
T1: The tumour is limited to the pancreas only, ≤ 2 centimetres in greatest dimension.
T2: The tumour is in the pancreas only, > 2 cm.
T3: The tumour extends beyond the pancreas, but without involving the celiac axis or superior mesenteric artery.
T4: The tumour extends beyond the pancreas into major arteries or veins near the pancreas and is unresectable.

The letter "N" is used for involvement of regional lymph nodes.

NX: The regional lymph nodes cannot be assessed.
N0: No regional lymph node metastasis.
N1: Regional lymph node metastasis.

The "M" in the TNM staging system indicates metastases, spreading of the cancer to other parts of the body.

M0: No distant metastasis.
M1: Distant metastasis.

1.1.3 Diagnostics

Pancreatic cancer is most commonly asymptomatic, especially when it is located in the body or tail area. But it can also present with abdominal or lower back pain, weight loss, fatigue or weakness. If the tumour hinders bile drainage, jaundice is also among the symptoms. With highly advanced malignancies symptoms can also come from metastasis. Pancreatic cancer typically spreads to the liver, to the peritoneal cavity and to the lungs.
No diagnostically significant markers are yet known for early stages. Tumour markers such as CEA or CA 19-9 are elevated in advanced tumours and more important in follow-up.
Sonography and endosonography are the most commonly used techniques in pancreas diagnostics. Endosonography provides higher resolution compared to conventional sonography. Typically, the symptom detected by this technique is the widening of both bile duct and pancreatic duct, known as *double duct sign*.
When the symptoms point to gallbladder disease, but are suspected to be caused by pancreas, the procedures indicated are endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP).
Computed tomography (CT) is used if for determination of tumour spread. When the tumour stage cannot be determined clearly with imaging techniques, diagnostic laparoscopy can be done for assessing the operability of the tumour.
When a tumour is found, fine-needle aspiration and biopsy are used to classify it. The same procedure is applied in case of infection of pancreatic necrosis. [10,13]

1.1.4 Therapy

When the diagnosis of carcinoma could not be established beforehand, a part of tissue is taken during the first stage of surgery. A histological analysis is performed immediately. Sometimes it is impossible to obtain representative tissue for histologic diagnosis, because most of the palpable mass may consist of inflamed pancreatic tissue. Tumour progression and its operability are determined with staging. If the tumour is operable, a resection is performed, followed by adjuvant chemotherapy. If the tumour is already too advanced, palliative chemotherapy is introduced or best supportive care measures are taken. [10]

1.1.4.1 Operative measures

For curable lesions tumour excision is required with a recommended safety distance of 2 centimetres. In most of the cases, however, pancreatic malignancies are already too advanced for this safety distance to be achieved.
Excision of the tumour is only possible in 10–20% of patients with tumours in the head of the pancreas. [11,14]

1.1.4.1.1 The Whipple procedure

The standard procedure for most of the tumours of the head of the pancreas is proximal pancreatoduodenectomy. It is also known as the Whipple procedure, named after the originator of the previous two-stage procedure. It involves removal of the gastric antrum, gall bladder, cystic duct, common bile duct, head of the pancreas, duodenum, proximal jejunum and also regional lymph nodes.
This treatment is effective because both the head of the pancreas and the duodenum are supplied with arterial blood from the gastroduodenal artery. Removal of only one component would result in tissue necrosis of the other part with the same blood supply.
To allow food, bile and digestive juices to pass, reconstruction of the digestive tract is needed. This is done by attaching pancreas, hepatic duct and stomach to jejunum.
This surgery is a major procedure and is carried out only in specialist centres. Mortality is less than 5%. [3,4,15,16]

1.1.4.1.2 Pylorus-sparing pancreatoduodenectomy

A variation of the Whipple procedure, pylorus-preserving pancreatoduodenectomy is becoming increasingly popular, since it spares the pylorus and the lower part of the stomach. Thus normal gastric emptying is preserved. The procedure also shows no survival impairment and faster recovery rate. [10,16]

1.1.4.1.3 Left-sided (distal) pancreatic resection

This procedure is indicated with tumours of the tail of the pancreas. Because the tail and the spleen have the same vascular supply it is usually impossible to preserve the spleen. [10]

1.1.4.2 Adjuvant therapy

Adjuvant therapy is a systemic therapy commonly used after complete resection with no demonstrable local or systemic disease. It consists of chemotherapy, radiation, immunotherapy or hormone therapy.
Nowadays this has become a standard procedure in most of the cancerous diseases, since it improves overall survival. [10]

1.1.4.3 Palliative therapy

When a tumour is not operable anymore, palliative care is introduced. This only alleviates the pain and improves the symptoms, but does not improve the prognosis.
Sometimes surgical intervention is required to achieve this, but only if the likelihood of improving the life quality is significant and risks are not too high.
If the tumour is unresectable, the passage of the bile can be established with percutaneously or endoscopically placed biliary stents. This procedure is also performed in patients with cholestasis prior to surgery to reduce the risk.
When the lesion blocks the duodenum, gastroenterostomy aims to re-establish the passage.

Pain management is induced with heavy analgesics, usually opioids. The pain is caused by invasion of the tumour into the coeliac plexus and can be also surgically blocked with alcohol at the time of the surgery. Another possibility is percutaneous blockage under radiological control. [10,14]

1.1.5 Prognosis

Pancreatic cancer is the fourth most common cause of cancer-related deaths and has one of the highest fatality rates of all cancers. Among the gastrointestinal tumours, it has the worst prognosis and outcome. [17]

Exocrine tumours have extremely poor prognosis, as there are usually no symptoms indicating that the tumour is locally advanced or has developed metastases. After the diagnosis the relative survival rate is 25% after 1 year and 6% after 5 years for all stages of malignant pancreatic cancer combined.

In tumours with slower progression the prognosis is better and patients, even if surgery is not possible, may live a couple of years. Endocrine tumours also permit much better outcome. [6,18]

1.2 Gallbladder

1.2.1 Anatomy, Histology, Physiology

1.2.1.1 Anatomy

The gallbladder is a 7 to 10 centimetres long, bulbous organ that sits in the gallbladder fossa, intraperitoneally at the right midclavicular line at the lower edge of the 9th rib, just beneath the right lobe of the liver, to which it is connected by connective tissue. It is divided into three sections: fundus, body and neck.
The neck lies at the medial end close to the porta hepatis and narrows before it connects to the biliary tree via the cystic duct. The latter joins with the common hepatic duct into the common bile duct, which ends in the duodenum. The neck widens at its lateral end. This widening is also called Hartmann's pouch and it is the location where gallstones commonly get stuck.
The body of the gallbladder normally lies in contact with the liver surface, anterior to the duodenum and the right end of the transverse colon.
The fundus lies at the lateral end of the body, very often in contact with the anterior abdominal wall. [1–3]

1.2.1.1.1 Vascular supply

Arterial blood is supplied to the gallbladder via the cystic artery that originates from the right branch of the proper hepatic artery in the cystohepatic triangle. Besides the gallbladder this artery also supplies the cystic duct. Here the cystic artery branches into two to four Calot's arteries that supply blood to the neck of the gallbladder and also to a part of the cystic duct.
The venous blood supply consists of numerous small veins that empty directly into the liver, and cystic veins that empty into the portal vein. [1,3,4]

1.2.1.1.2 Lymphatic drainage

Most of the lymph vessels of the gallbladder drain to hepatic lymph nodes, often via the cystic lymph node, next to the hepatic portal vein, and celiac lymph nodes, next to the celiac artery. [3]

1.2.1.1.3 Innervation

The autonomic innervation of gallbladder and bile ducts originates in the hepatic plexus, which is the largest offset from the celiac plexus. It receives nerve fibres from the vagus and phrenic nerves. The stimulation of the gallbladder intensifies the hormonally induced contraction of the muscles of the gallbladder. [3]

1.2.1.2 Histology

The gallbladder wall is built of three layers: *mucous membrane*, *muscular layer*, *tela subserosa* with *tunica externa*. The wall does not, as it is usual in other organs, consist of a serous membrane, but the function of a layer, separating and protecting it from the liver, is taken over by the *tunica externa*.
The innermost layer, the mucous membrane, is like a net of interconnected different levels of wrinkles. It consists of resorbable *simple columnar epithelium with brush border membrane* (microvilli-covered surface), which sits on a thin layer of loose connective tissue called *lamina propria*.
The muscular layer is composed of fibrous connective tissue and mixed with interlacing smooth muscle cells.
Tela subserosa is another layer of connective tissue and *tunica externa* is the outer cover of the gallbladder, which comes from the peritoneum. [2,5]

1.2.1.3 Physiology

The gallbladder can store about 50 millilitres of bile and has high water absorption capacity due to the enzyme Na^+/K^+-ATPase, which enables active transport of water out of the gallbladder. The concentrated bile has increased potency to emulsify fats in partly digested food.
Bile consists of bile acids, cholesterol, phospholipids (lecithin) and the bile pigment bilirubin, a product of haemoglobin degradation, which gives the bile its typical yellow colour. It also contains Na^+, K^+, Cl^-, HCO_3^-, mucus and water. Bile is mostly produced in the liver, where between 500 and 800 millilitres of primary bile is synthesised per day and drains from hepatocytes via the smallest bile vessels to interlobular bile ducts and hepatic ducts. From here the bile drains to the gallbladder via cystic duct.
During ingestion, when food rich in fat enters the digestive tract, the smooth muscles of the gallbladder contract and squirt the bile via the cystic and the common bile ducts to the small intestine, where bile is needed to emulsify the fats. [4,10]

1.2.2 Inflammation

1.2.2.1 Acute cholecystitis

Acute cholecystitis usually occurs due to blockage of the bile duct caused by gallstones. This causes bile to accumulate and concentrate in the gallbladder and consequently the pressure in the gallbladder to increase. Intestinal bacteria can invade and irritate the previously damaged organ. All this combined with toxic chemical effects of bile acids irritates and damages the gallbladder wall, causing redness, oedema and small bleedings. Ulcerative mucosal defects can be present as well. The gallbladder is usually filled with fibrinous-purulent haemorrhagic exudate.
Possible complications are: spread of the inflammatory process to the other organs or perforation into the free abdominal cavity, fistula between the gallbladder and intestine, collection of pus in the bladder, or, after the abated inflammation, fibrosis of the gallbladder and loss of contractile capability. [6]

1.2.2.2 Chronic cholecystitis

Chronic cholecystitis is the most common disease of the gallbladder. It can develop lingering or due to repeated acute inflammations, caused by the same pathogens as acute cholecystitis.
The morphological signs are thickened and fibrotic gallbladder wall and scarred and atrophic (and additionally hyperplastic) mucous membrane. When fibrosis is pronounced and combined with dystrophic calcification, this morphological variant is called porcelain gallbladder. [6]

1.2.3 Gallstones

Gallstones are crystalline concretions that develop in gallbladder or extra- or intrahepatic bile ducts as an accretion of bile components: bile acids, cholesterol, phospholipids, bilirubin and proteins.
Since the solubility of these components depends on the salt concentration, already the smallest change in the bile composition or irritation of the gallbladder such as infection or stenosis can influence and start the formation of gallstones.
The gallstones may consist of cholesterol, pigment and rarely calcium carbonate. Most commonly, the stones are mixed and present with a heterogenic intersection.
Very often gallstones do not cause any symptoms and therefore do not need any medical treatment. On the other hand, they can block one of the ducts and lead to acute and later even chronic inflammation of gallbladder or bile ducts, development of ulcerations, or perforation into the free abdominal cavity. [6,19–21]

1.2.4 Cholestasis

Cholestasis is a reduction or complete abolition of bile flow, which causes increased concentration of bile components in the blood.
The disorder leading to cholestasis can lie at any point between bile production in liver cells and the confluence of the bile duct into the duodenum. Two basic distinctions of cholestasis are obstructive and non-obstructive type.
In non-obstructive cholestasis the flow of the bile from hepatocytes into the capillary vessels is disturbed. The interference lies in the transport proteins, canalicular membrane of the hepatocytes, congenital defects of the enzymes or alteration in intracellular organelle function. It can also appear as an accompanying disease or following certain conditions, such as viral hepatitis, pregnancy, alcoholic fatty liver or as side effect of some medications.
The obstructive form occurs in case of mechanical blockage, which prevents the bile from draining. The obstruction can occur intrahepatically from liver malignancy or extrahepatically from gallstones.
Another consequence of cholestasis is maldigestion of fats in the intestines due to missing bile acids. Moreover, the fat-soluble vitamins undergo inadequate absorption.
Cholestasis can also cause liver cirrhosis. [8,10,22]

1.2.5 Diagnostics

Patients with gallbladder problems usually describe colicky pain in the upper right part of the abdomen that possibly radiates to the back or the shoulder. It is crucial to confirm that the pain comes from the gallbladder and is not caused by another condition.
The examination starts with anamnesis and physical examination. The classic symptoms are constant and severe pain in the upper right part of the abdomen, but can also be absent in cases of gallstones or chronic inflammation of the gallbladder. The pain often occurs after meals and is accompanied by nausea, vomiting, dizziness or bloating. Imaging techniques are necessary to confirm the diagnosis. There is usually no tenderness in chronic cholecystitis.

Gallbladder problems are diagnosed through various tests. Basic examinations that support the diagnosis are laboratory tests and sonography. In special cases it is also possible to resort to other examinations.
Blood diagnostics shows leucocytosis or elevated C-reactive protein (CRP) values in case of inflammatory disease, or elevated levels of gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP) or direct bilirubin when cholestasis is suspected. In case of gallstones, any of these values can be elevated, depending on the complications.
Sonography is a noninvasive imaging technique, which uses sound waves that reflect from the anatomic structures to provide the information about gallbladder content and texture of its wall. [10,20,21]

1.2.5.1 Inflammation markers

When there is tissue damage or penetration of foreign bodies, the cells release cytokines locally. These cytokines make the surrounding cells alert of the disorder, which consequently leads to the body's defence response, an inflammation.
Besides the local reaction these cytokines also trigger systemic reactions by flowing in the blood stream. If they reach the liver, they induce the synthesis of many proteins, also called acute-phase proteins: coagulation factors, protease inhibitors and metal-binding proteins. [4,23]

1.2.5.1.1 C-reactive protein

C-reactive protein (CRP) is another acute-phase protein synthesized by the liver and it is one of the most important markers in clinical diagnosis of inflammation. Its name stems from its ability to react with C-polysaccharides of *Streptococcus pneumoniae.*
The physiological role of CRP is to bind the phosphocholine on the surface of damaged or dead cells (or some types of bacteria) and activate the complement system, enhancing the phagocytosis by macrophages.
The normal level of CRP in blood is lower than 10 $^{mg}/_{l}$. It is measured in blood in order to define the source of infections or inflammation and for follow-up. While bacterial infections cause this value to rise abnormally, viral infections have little to none effect on

it. The level of CRP rapidly increases during the acute-phase response within 6 hours and reaches its peak after 48 hours. The elevated level also declines rapidly when the inflammation is resolved: the half-life of CRP in blood is 18 hours. Because its half-life is constant, we can approximate that its level is mainly determined by the rate of synthesis of the protein.
Because of the variety of causes that encourage the CRP production, its clinical significance does not lie in the diagnostics of specific illnesses, but it is only one of the fragments marking the presence of an inflammatory disease. [4,23]

1.2.5.1.2 Leukocytes

Leukocytes (white blood cells) are parts of the immune system, which protect the body against penetration of foreign bodies and infectious illnesses. Pluripotent haematopoietic stem cells are produced in the bone marrow and then differentiate to various cell types. These are morphologically and functionally different, but they all have important roles in the immune system. They are distinguished by simple morphological criteria (cell size, size and form of the nucleus, presence of granula and their ability of dye absorption) into granulocytes, lymphocytes and monocytes, of which granulocytes are further subdivided to neutrophils, eosinophils and basophils.
Another possible differentiation of the cells relies on the expression of antigen proteins, the significant markers on the surface of the white blood cells. They can be detected by flow cytometry (a laser-based method) and classified in accordance with the CD-system.
The leukocytes have three main functions: defence, disposal and emigration. Defence function is activated by any foreign material that penetrates in the body, even if it is harmless, and concludes with its elimination. Also altered endogenous material, for example damaged, degenerated or dead cells, is identified, dismantled and discarded by leukocytes, which thus fulfil their disposal function. Both of these cell functions are completed outside the blood stream. The third function, emigration, is needed to actively immigrate from the blood stream into the extravascular space.
Different white blood cell types can be classified by their operating modes. Neutrophil granulocytes and monocytes are phagocytes. Eosinophil granulocytes are activated by antigen-IgE complexes and serve as defence against parasites. The basophil granulocytes play an important role in activation and coordination of inflammation, especially with

allergies, since they release histamine. Lymphocytes are carriers of specific immune reactions by formation of antibodies and cytotoxic killer function.
The concentration of all white blood cells in a healthy individual is between 4.400 and 11.300 cells per microlitre of blood. These cells live three to four days and are found throughout the body. Both elevation, also called leucocytosis, and depression, also called leukopenia, of the white blood cells are often indicators of disease. Besides the cell number, changes may also occur in cell volume, granularity or conductivity due to the presence of malignant leukocytes or immature cells. [4,23]

1.2.5.2 Cholestasis markers

The enzymes that are normally secreted to the bile occur in blood due to cholestasis. These enzymes are ALP, GGT and leucine arylamidase (LAP). Therefore, especially ALP and GGT are very important blood components in diagnostics of biliary tract disease and they correlate well. It is not known yet which of these has better sensitivity. For historical reasons, ALP is the first test for biliary disease, but this has to be confirmed by an elevated value of GGT. If the ALP value is increased and the GGT remains low, this excludes biliary disease.
In cholestasis not only the enzymes but also other bile constituents are retained, mostly cholesterol and bile acids. The retention of bile acids results in increased bile acid concentration in the skin, which is the main reason for generalized itching.
Concentration of direct bilirubin is also elevated in cholestasis. Similarly to ALP and GGT, it is over-concentrated in the gallbladder; so it enters the blood stream and is eliminated via the kidneys. Besides the elevated blood values of direct bilirubin, its renal elimination also results in darker urine and brighter stool due to the lack of the bilirubin degradation products urobilin and stercobilin on the other side. [4,23]

1.2.5.2.1 Gamma-glutamyltransferase

Gamma-glutamyltransferase (GGT) is an enzyme that consists of two polypeptide chains, a heavy and a light subunit; the active site is located on the light chain. The enzyme is involved in transport of amino acids across the cellular membrane, leukotriene metabolism

and glutathione metabolism: it transfers the gamma-glutamyl moiety of glutathione to different acceptor molecules, such as amino acids, peptides or water, in which case it forms glutamate. [4,23]
The highest concentration of GGT is in the cell membrane of liver cells, but it is also present in kidneys, pancreas, gallbladder, biliary tree, spleen and heart. [24] In medicine it is of great significance, as it is an important diagnostic marker. Normal blood level is under 40 $^{IU}/_{l}$ for women and under 60 $^{UI}/_{l}$ for men. [10] Elevated values can point to diseases of the liver, biliary tract or pancreas.
GGT also accumulates in atherosclerotic plaques and has recently been correlated with cardiovascular diseases. [25] High serum GGT is associated with patients with type 2 diabetes who have high BMI [26] and is also increased after heavy alcohol consumption. Alcohol abuse or consequential liver diseases result in isolated GGT elevation, while other liver enzymes (for example ALP) are within the normal range. This is possibly due to increased GGT production or to leakage of GGT from hepatocyteslea. [27]
Raise in GGT levels can also be the consequence of the use of certain medications, for example antiepileptic phenytoin or aspirin.

1.2.5.2.2 Alkaline phosphatase

Alkaline phosphatase (ALP) is a hydrolase enzyme that is responsible for dephosphorylation in alkaline pH. This is a process of removing phosphate groups from many different types of molecules, such as proteins, alkaloids or nucleotides. In humans the enzyme is present in all body tissues, with the highest concentration in bones, kidneys, liver, bile duct and placenta.
The normal blood level of ALP ranges from 20 to 140 $^{IU}/_{l}$ [10] and it is mainly used as a sensitive indicator of cholestasis. Increased values can indicate obstruction of bile ducts or active bone formation, because ALP is a byproduct of osteoblasts. Elevated blood levels of ALP are also common in children, pregnant women and patients with untreated coeliac disease, but it is not associated with health risks.
Lower levels of ALP can also indicate some diseases, but are not as common as elevated levels. [4,17,23]

1.2.5.2.3 Bilirubin

Bilirubin is a yellow breakdown product of normal haem catabolism. Haem is a prosthetic group of haemoglobin, a principal component of red blood cells.
The degradation of haem occurs in the mononuclear phagocyte system. Haem oxygenase oxidizes haem to biliverdin, and biliverdin reductase reduces biliverdin to bilirubin. Chemically, bilirubin consists of an open chain of four pyrrole-like rings (tetrapyrrole).
The solubility of bilirubin in water is very poor, so the blood transport to the liver is facilitated by albumin that binds the bilirubin and increases its solubility. This complex is called *indirect bilirubin*, since it can only be measured when albumin has been chemically removed. When indirect bilirubin reaches the liver, bilirubin and albumin are separated in the sinusoids. Bilirubin then enters the hepatocytes.
In hepatocytes bilirubin undergoes oxidative reactions that increase polarity and solubility, so that it ultimately can be excreted with the bile as bile pigment. This end product is bilirubin diglucoronide.
This conjugated bilirubin in the liver is named *direct bilirubin*, because it can be measured without modifications in the clinical-chemical laboratory. The difference between indirect and direct bilirubin is of great importance, because in disorders of haemoglobin degradation the type of elevated bilirubin can point to the type and localisation of the damage.
Bilirubin is excreted from the liver to the gallbladder and small intestine. Bilirubin diglucoronide is highly concentrated in the gallbladder and in the smallest bile ducts; so it needs to be actively transported from the hepatocytes. This is the slowest and therefore rate-determining step of the whole bilirubin degradation.
Bilirubin diglucoronide reaches the small intestines with the bile. Intestinal bacteria complete the last steps in the bile degradation when they cleave the glucoronic acid from bilirubin diglucoronide with the enzyme ß-glucoronidase. The same colonic bacteria oxygenise bilirubin to form colourless urobilinogen.
A small amount of urobilinogen is excreted either in urine, where it oxidates to urobilin, giving the urine its yellow colour, and in faeces, where it is degraded to stercobilin, giving the faeces its brown colour. However, most of the bilirubin degradation product urobilinogen is reabsorbed into the portal blood and thus into the enterohepatic circulation. From portal blood the most of the urobilinogen re-enters the hepatocytes, which excrete it

again into the bile. The molecules of urobilinogen that were not reabsorbed by hepatocytes enter the systemic circulation. [4,10,23]

The normal level of total bilirubin in blood is lower than 1 $^{mg}/_{dl}$. If the concentration gets higher, bilirubin diffuses in tissues and colours them yellow. This is known as icterus. It is usually seen best on the sclera of the eyes, where it becomes visible already with a concentration above 1.2 $^{mg}/_{dl}$, while the skin does not get coloured at bilirubin levels below 2.0 $^{mg}/_{dl}$. [10]
A range of disorders in the bilirubin production can cause elevated levels and consequently icterus. Problematic excretion of bilirubin is determined by elevated direct bilirubin level. If the problem lies already in the liver or even before the liver, the level of indirect bilirubin is elevated. [10]

1.2.6 Therapy

Fasting in combination with antispasmodics, analgesics and systemic antibiotics are first-line therapy for acute inflamed gallbladder. The inflammation is mostly due to gallstones, which, once symptomatic, usually are recurrent and therefore removed. First-line therapy nowadays is laparoscopic cholecystectomy, which can be replaced by conventional surgical intervention if laparoscopy is not possible. Oral cholelitholysis or extracorporeal shock wave lithotripsy are used with high-risk patients or in case of patient's refusal of surgery, but are not common due to high recurrence rates and lower success when compared to surgery.
Chronic inflammation of the gallbladder usually leads to preventive cholecystectomy since persistent inflammation is a risk for the development of malignant growth on the gallbladder.
The therapy of the cholestasis depends on the cause of the disease. With obstructive cholestasis the outflow barrier should be removed endoscopically or surgically if the first option is not possible or there are complications. [10,13,28,29]

1.2.7 Prognosis

The lethality of cholecystectomy lies between 0.5 and 3.0%. It is greatly influenced by the patients' age, but generally it can be stated that the lethality of the early surgeries lies just slightly above elective procedures. However, it is increased with every further complication like perforated gallbladder or peritonitis.
One third of the patients the symptoms persist even after cholecystectomy. This is known as *postcholecystectomy syndrome* and is mostly ascribed to post-surgical adhesions, remaining stone(s) or any other biliary injury. [6,10]

2 Materials and Methods

2.1 Materials

This evaluation comprised data of 565 patients who were treated for malignant diseases of the pancreas at the Department of General Surgery of the Medical University of Graz in the period between May 2000 and May 2010.
Electronic patient data were analysed retrospectively, including basic pancreatic risk factors such as female sex, age above 50 and adiposity. To document the link between findings in the gallbladder and pancreatic lesions we focused also on the localization of the pancreatic lesions, accompanying pancreatic changes, type of the surgery performed, gallbladder changes and presence of gallstones. To determine types and extent of changes in the gallbladder, five laboratory parameters were analysed: leukocytes and CRP as parameters for inflammation, and total bilirubin, GGT and ALP as liver parameters for cholestasis.

2.2 Methods

All patient data were analysed statistically using the Microsoft Excel 2011 software, version 14.3.4. For a general overview, we evaluated the following parameters: time period, age, sex, height and weight of the patients, type and localization of pancreatic lesions and types of surgeries. We tested for correlation between these parameters, changes in the gallbladder, inflammation parameters (leukocyte count, CRP) and cholestasis (total bilirubin, GGT, ALP).

2.2.1 Inclusion criteria

In this retrospective research we included all the patients that underwent surgery at the Department of General Surgery of the Medical University of Graz for pancreatic lesions in the period between May 2000 and May 2010 and

- were diagnosed with a primary malignant pancreatic lesion;
- had an additional diagnosis of the gallbladder in the electronic patient data;
- had inflammation parameters (elevated leukocyte count, CRP) and cholestasis (elevated total bilirubin, GGT, ALP) in their electronic patient data;
- were more than 18 years old at the time of the surgery.

2.2.2 Exclusion criteria

We excluded patients that

- had secondary malignant pancreatic lesions.

3 Results

3.1 Demographics of the patients

At the Department of General Surgery of the Medical University of Graz 565 patients underwent surgery due to pancreatic lesions in the period between May 2000 and May 2010 *(Chart 1a)*. In our research we included basic risk factors and parameters to calculate other risk factors included sex (*Chart 1b*), age (*Chart 1c*), height (*Chart 2a*) and weight (*Chart 2b*) of the patients.

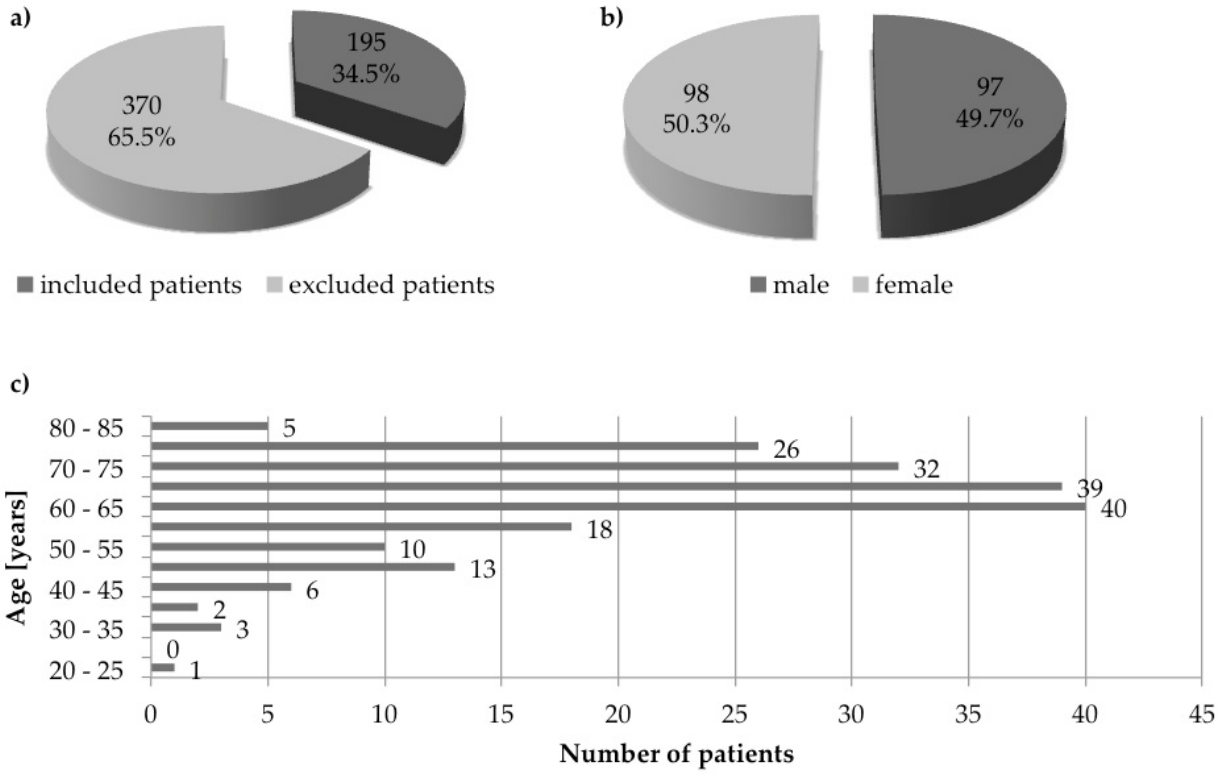

Chart 1: (a) Included/excluded patients; distribution of (b) sex and (c) age.

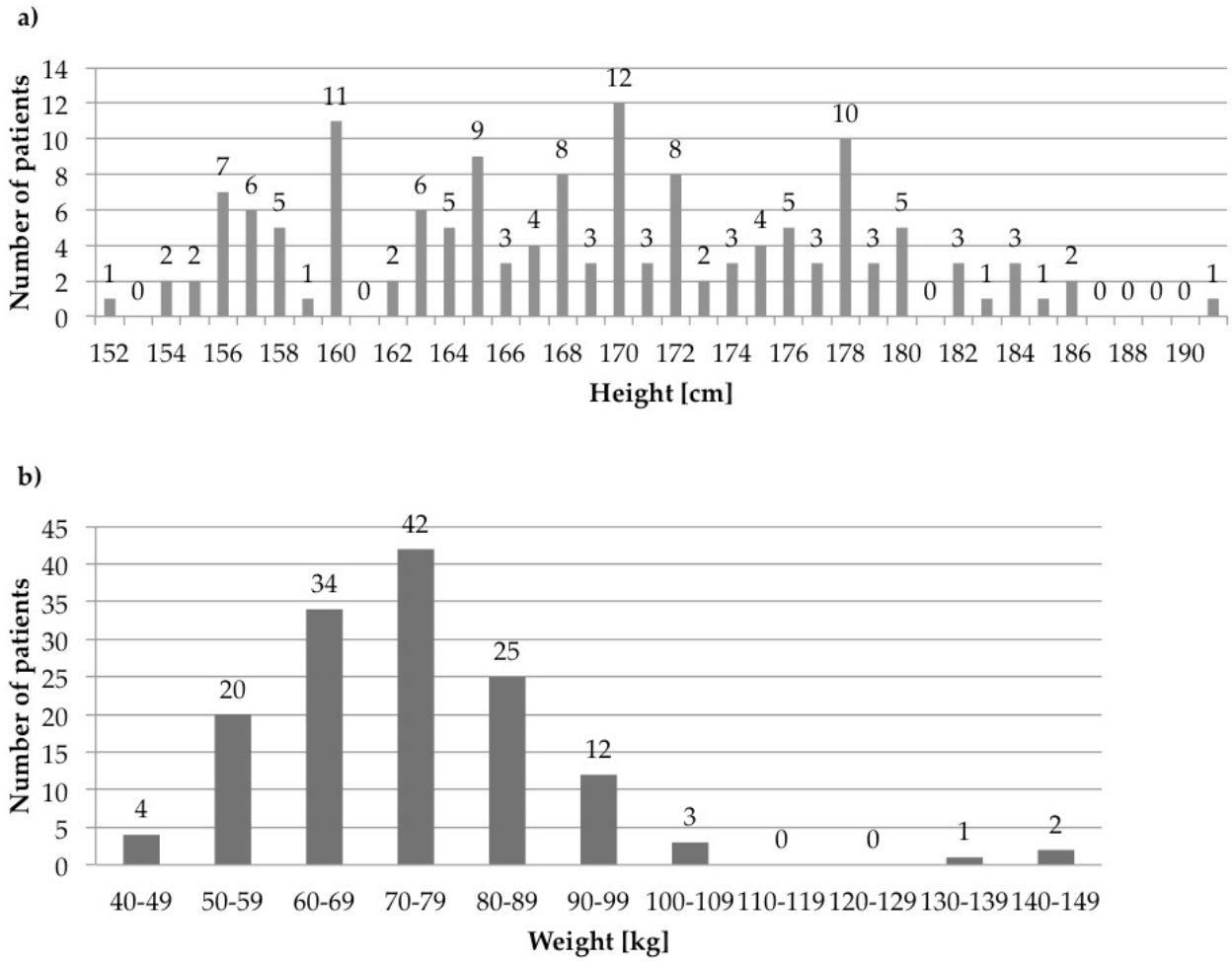

Chart 2: Distribution of (a) height and (b) weight.

3.2 Body mass index of the patients

The body mass index (BMI) is a measure of body shape, calculated as body mass divided by the square of the height with the unit $^{kg}/_{m2}$. It is designed as indicator of body fatness, classifying the population with average body composition.

Of the 195 patients included, it was not possible to obtain BMI values of 54 (27.5%) patients due to missing height or weight data *(Chart 3)*.

The World Health Organisation (WHO) regards a BMI of less than 15.0 as very severely underweight and a BMI between 15.0 and 16.0 as severely underweight. None of our patients fit into any of these two categories. A BMI between 16.0 and 18.5 classifies as underweight and corresponds to 1.0% of the patients. All 3 categories may indicate malnutrition or other health problems.

Normal BMI ranges from 18.5 to 25.0. Sixty-eight patients (35.0%) fit into the category of normal BMI.

A BMI greater than 25.0 is considered overweight and above 30.0 obese. Obesity is divided into 3 further classes: class I (BMI 30.0-35.0), class II (BMI 35.0-40.0) and class III (BMI greater than 40.0). While a third of patients have normal BMI, a number of 71 patients (36.5%) who are overweight or obese is an alarming fact.

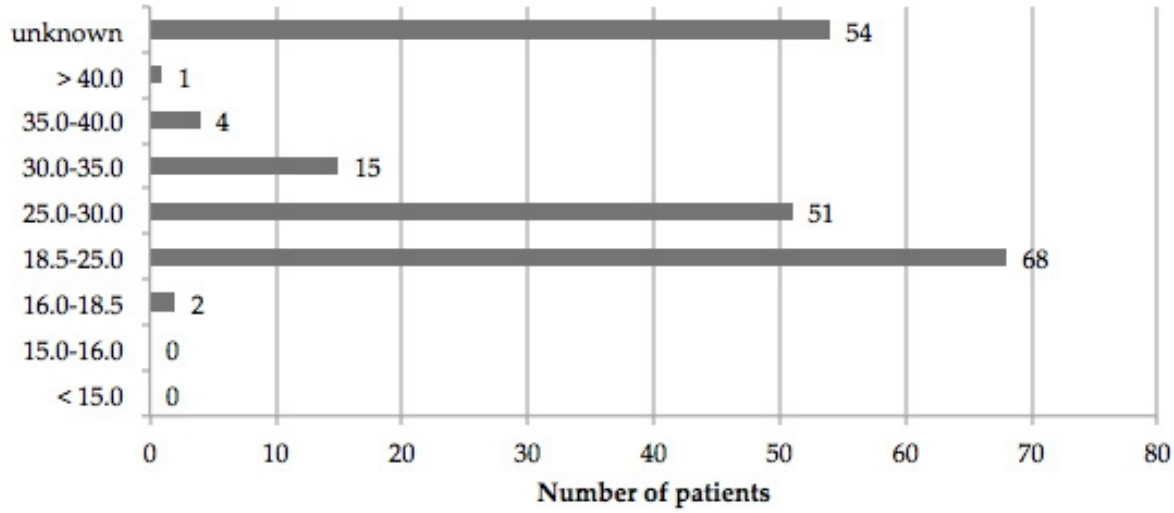

Chart 3: BMI distribution of patients.

3.3 Localisation of pancreatic lesions

The majority of the patients (78.0%) had pancreatic lesions only in the right side of the pancreatic gland *(Chart 4)*. Some patients had lesions in the left part of the pancreas or in both parts. In 5.0% of patients, the localisation of the pancreatic lesions was unknown.

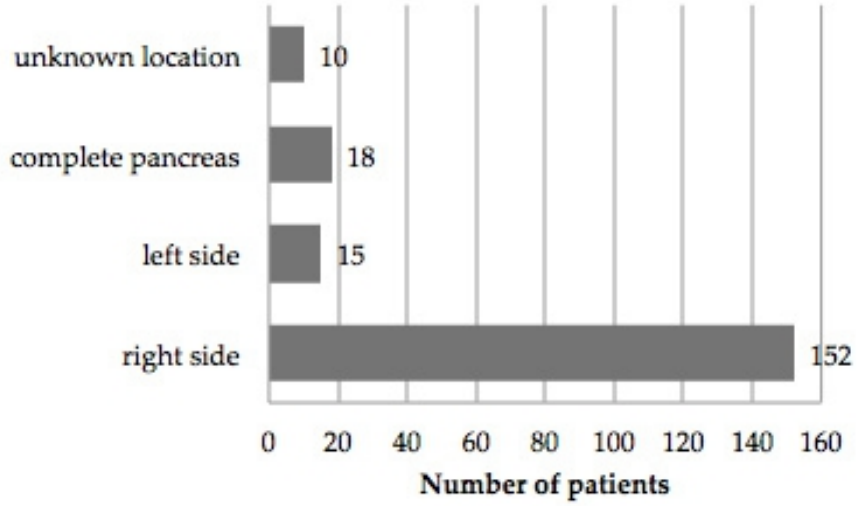

Chart 4: Localisation of pancreatic lesions.

3.4 Accompanying pancreatic and other lesions

Twenty-five (13.0%) patients had at least one accompanying pancreatic lesion besides the main tumour in the pancreas *(Chart 5)*: predominantly acute or necrotic pancreatitis and chronic or diffuse pancreatitis, but also pancreatic pseudocysts and pancreatic fistulas. Thirteen (6.5%) patients had other pathologic findings in the abdominal cavity: duodenal carcinomas and Klatskin tumours. Some patients had already developed liver metastasis and peritoneal carcinomatosis.

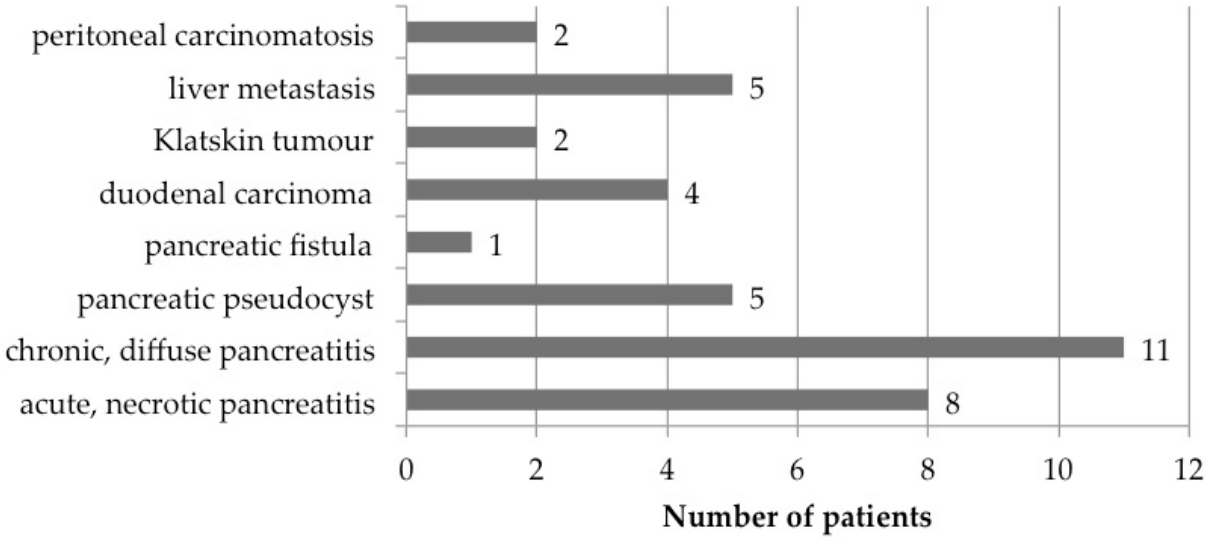

Chart 5: Accompanying pancreatic and other pathologic findings.

3.5 Types of surgeries

The majority of the patients (63.0%) underwent proximal pancreatoduodenectomy: approximately half of those patients underwent the classic Whipple procedure and the second half underwent pylorus-sparing pancreatoduodenectomy *(Chart 6)*. The rest of the patients underwent left-sided (distal) pancreatic resection, total pancreatectomy, explorative laparotomy, drainage and/or necrectomy or received palliative surgical intervention in form of different anastomoses.

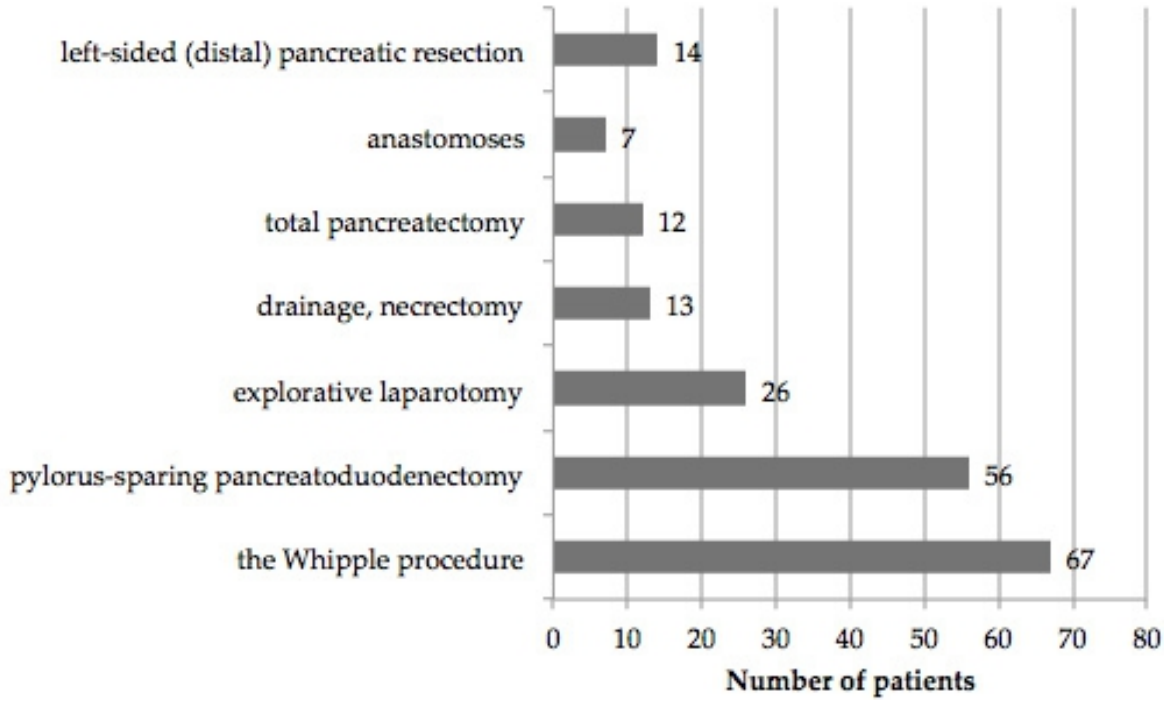

Chart 6: Distribution of types of surgeries performed on patients with primary malignant pancreatic lesions.

3.6 Accompanying gallbladder lesions

Of the 195 patients included in the study, the gallbladders of 39 (20.0%) patients were normal, 2 (1.0%) patients presented with acute inflammation and 22 (11.5%) patients with chronic-active inflammation. The majority of the patients (43.5%) had chronic inflamed gallbladder, while 43 (22.0%) presented with residues of previous cholecystitis. Four (2.0%) patients were diagnosed with cholangiocarcinoma (adenocarcinoma) or adenocarcinoma of gallbladder (*Chart 7a*).

Besides these diagnoses, 10 (5.0%) patients additionally had gallstones, most of them (90.0%) with chronic-active inflammation and only 1 (10.0%) with chronic inflammation (*Chart 7b*).

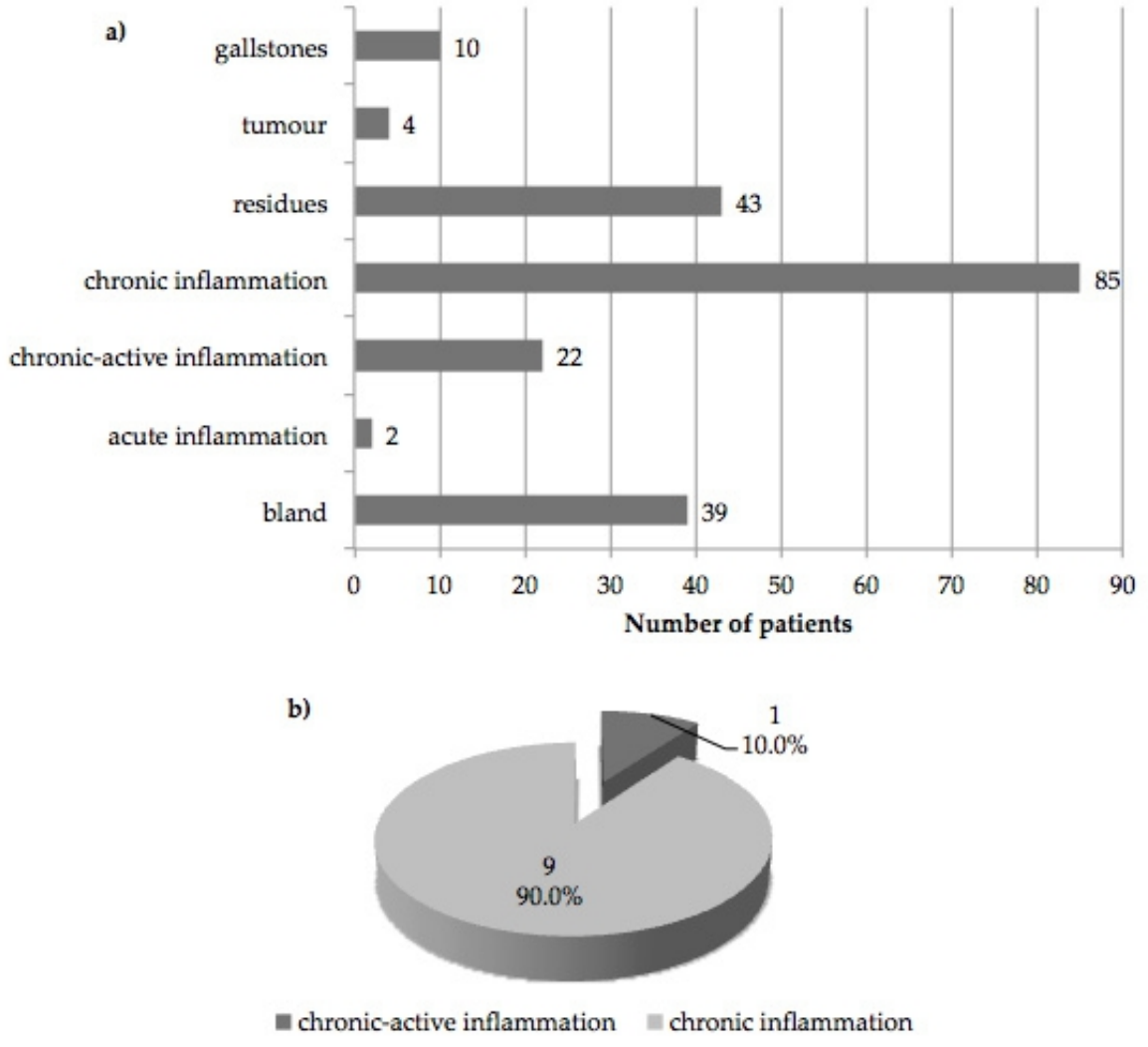

Chart 7: (a) Accompanying gallbladder lesions and (b) distribution of gallstones.

3.7 Inflammation markers

Of the 195 patients included, it was not possible to obtain CRP values of 15 (7.5%) patients *(Chart 8)*.

For our research we used normal ranges as valid at the Department of General Surgery of the Medical University of Graz. CRP values below 8.0 $^{mg}/_{l}$ are considered normal, while values above this mark are considered elevated.

Around half of the patients (49.5%) had normal CRP values in the last laboratory blood test, but only 14 patients less had elevated levels (*Chart 8a*).

The normal value of total White Blood Cell Count in adults at the Department of General Surgery of the Medical University of Graz is 4.4-11.3 $x10^{3\ cells}/_{\mu l\ of\ blood}$. In *Chart 8,* values above 11.3 $x10^{3\ cells}/_{\mu l\ of\ blood}$ (leucocytosis) are marked with "higher" while values less than 4.4 $x10^{3\ cells}/_{\mu l\ of\ blood}$ (leukopenia) are marked with "lower".

While it was not possible to obtain total white blood cell counts of 18 patients, the majority of the patients (75.0%) tested with normal levels of leukocytes (*Chart 8b*).

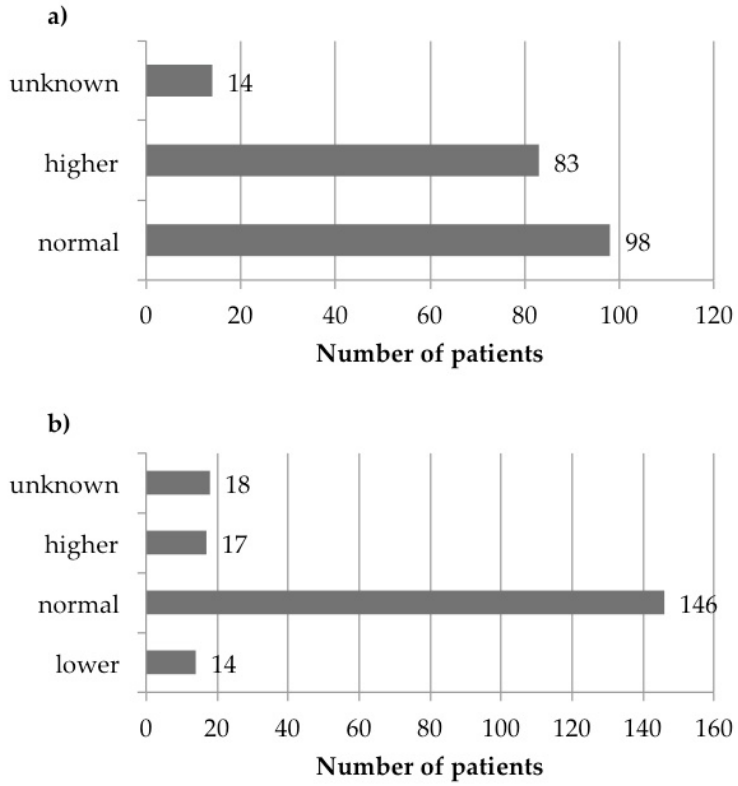

Chart 8: Distribution of values of inflammation markers: (a) C-reactive protein and (b) leukocytes.

3.7.1 C-reactive protein

Of the 195 patients included in this study, 98 (50.5%) patients presented with normal CRP value, which is rated as below 8.0 $^{mg}/_{l}$ at the Department of General Surgery of the Medical University of Graz (*Chart 8a*). The arithmetic mean of CRP value of all the patients with valid values was 29.4 $^{mg}/_{l}$, meaning 139 (77.0%%) of all patients with a measured CRP value presented with a value below and 42 (23.0%) with a value above this arithmetic mean.

The arithmetic mean of the patients with CRP values in the normal range is 3.2 $^{mg}/_{l}$. The minimum measured level of CRP was 0.0 $^{mg}/_{l}$ (3.2 $^{mg}/_{l}$ under the average value, also the lowest value possible measured) and the maximum level of CRP in patients with normal values was at 7.8 $^{mg}/_{l}$ (4.6 $^{mg}/_{l}$ above and almost 2.5 times above average value). The exact average value was measured in 2 (1.0%) patients, while most of the other patients (52.0%) had values below the average.

The arithmetic mean of the patients with elevated CRP value is 60.3 $^{mg}/_{l}$. The minimum measured level of CRP in patients with elevated values was 9.4 $^{mg}/_{l}$ (50.9 $^{mg}/_{l}$ under and almost 6.5 times below the average value) and the maximum value was at 484.4 $^{mg}/_{l}$ (just above 8 times more than the average value, but also over 60 times more than the upper limit). Most of these patients (73.5%) had CRP values below the average.

3.7.2 Leukocyte count

Of the 195 patients included in the study, 146 (75.0%) patients presented with normal leukocyte value, which is 4.4-11.3 $x10^3$ cells per microlitre of blood at the Department of General Surgery of the Medical University of Graz (*Chart 8b*). The arithmetic mean of leukocyte count of all the patients with measured values was 7.7 $x10^{3\ cells}/_{\mu l\ of\ blood}$, meaning almost two thirds (62.0%) of all patients with valid leukocyte count presented with a value below and more than one third (36.5%) with a value above this arithmetic mean, while 2 (1.0%) patients had exactly the average value.

The arithmetic mean of the patients with leukocyte values in the normal range is 7.0 $x10^{3\ cells}/_{\mu l\ of\ blood}$. The minimum measured level of leukocytes was 4.4 $x10^{3\ cells}/_{\mu l\ of\ blood}$ (2.6 $x10^3$ cells under and almost 1.6 times below the average value, also the lowest

measured value possible to still qualify as normal), which was measured in 2 (1.0%) patients. The maximum level of leukocytes in patients with normal values was at 11.3 $x10^3$ $^{cells}/_{\mu l\ of\ blood}$ (4.3 $x10^3$ cells above and more than 1.6 times above average value, also the highest measured value possible to still qualify as normal). Most of the patients (55.5%) had values lower of the average.

The arithmetic mean of the patients with elevated leukocyte value is 17.1 $x10^{3\ cells}/_{\mu l\ of\ blood}$. The minimum measured level of leukocytes in patients with elevated values was 11.5 $x10^{3\ cells}/_{\mu l\ of\ blood}$ (5.6 $x10^{3\ cells}/_{\mu l\ of\ blood}$ under and almost 1.5 times below average value) and the maximum value was at 47.4 $x10^{3\ cells}/_{\mu l\ of\ blood}$ (30.3 $x10^{3\ cells}/_{\mu l\ of\ blood}$ above and approximately 2.8 times above average value, but also almost 4.2 times more than the upper limit). Most of these patients (82.5%) had values below the average.

The arithmetic mean of the patients with lower leukocyte value is 3.8 $x10^{3\ cells}/_{\mu l\ of\ blood}$. The minimum measured level of leukocytes was 3.0 $x10^{3\ cells}/_{\mu l\ of\ blood}$ (0.8 $x10^{3\ cells}/_{\mu l\ of\ blood}$ under and approximately 1.3 times average value) and the maximum value in the patients with lower value of leukocytes was at 4.2 $x10^{3\ cells}/_{\mu l\ of\ blood}$ (0.4 $x10^{3\ cells}/_{\mu l\ of\ blood}$ above and approximately 10% above the average value), which was measured in 3 (21.5%) patients. The number of patients with lower and higher values than average is distributed equally.

3.8 Cholestasis markers

In *Chart 9,* the blood values displayed are those of the enzymes GGT, ALP and total bilirubin, which we observed in our research.

While the standard normal blood level of GGT is under 40 $^{IU}/_{l}$ for women and less than 60 $^{UI}/_{l}$ for men, standardised normal laboratory values of less than 55 $^{UI}/_{l}$ for both sexes are used at the Department of General Surgery of the Medical University of Graz. Of the 195 patients included in the study, it was not possible to obtain GGT values of 14 (7.0%) patients, but it is still evident that most of the patients (72.0%) have GGT levels above 55 $^{UI}/_{l}$ (*Chart 9a*).

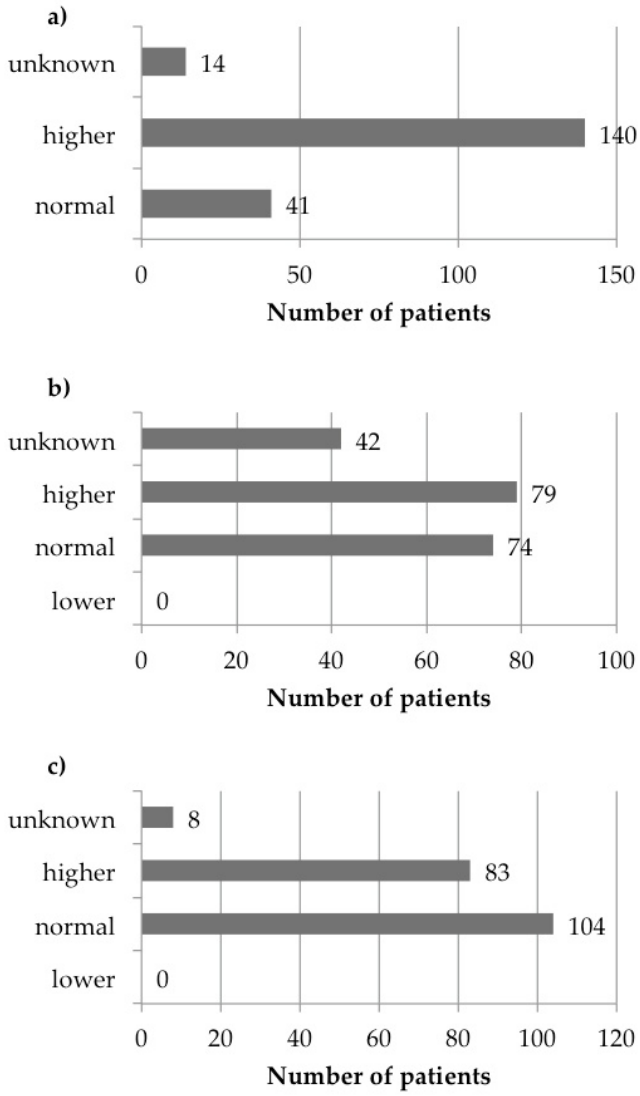

Chart 9: Distribution of values of cholestasis parameters: (a) gamma-glutamyltransferase, (b) alkaline phosphatase and (c) total bilirubin.

The normal blood level of ALP ranges from 20 to 140 $^{UI}/_{l}$, but the laboratory of the Department of General Surgery of the Medical University of Graz marks method-specific values between 40 and 130 $^{UI}/_{l}$ as normal. Of the 195 patients included, it was not possible to obtain ALP values of 42 (21.5%) patients and none of them had an ALP level below 40 $^{UI}/_{l}$ (*Chart 9b*).
The normal range of total bilirubin at the Department of General Surgery of the Medical University of Graz is 0.1-1.2 $^{mg}/_{dl}$. Most of the patients' (53.5%) total bilirubin levels are in this area and none presented with levels under 0.1 $^{mg}/_{dl}$. It was not possible to obtain data of 8 (4.0%) patients (*Chart 9c*).

3.8.1 Gamma-glutamyltransferase

Of the 195 patients included, 41 (21.0%) patients presented with normal GGT value, which is standardised as less than 55 $^{UI}/_{l}$ for both sexes at the Department of General Surgery of the Medical University of Graz (*Chart 9a*). The arithmetic mean of GGT value of all the patients with measured values was 346 $^{UI}/_{l}$, meaning the majority (72.0%) of all patients with measured GGT value presented with a value below and 50 (27.5%) with a value above this arithmetic mean, while one (0.5%) patient had exactly the average value.
The arithmetic mean of the patients with GGT values in the normal range is 27 $^{UI}/_{l}$. The minimum measured level of GGT was 4 $^{UI}/_{l}$ (23 $^{UI}/_{l}$ under and almost 7 times below average value) and the maximum level of GGT in patients with normal value was at 53 $^{UI}/_{l}$ (26 $^{UI}/_{l}$ above and almost 2 times above average value). Most of these patients (61.0%) had values below average.
The arithmetic mean of the patients with elevated GGT value is 440 $^{UI}/_{l}$. The minimum measured level of GGT in patients with elevated value was 56 $^{UI}/_{l}$ (384 $^{UI}/_{l}$ under and almost 8 times below average value), which was measured in 2 (1.0%) patients. The maximum measured level was at 2851 $^{UI}/l$ (2411 $^{UI}/l$ above and approximately 6.5 times above average value, but also almost 52 times above upper limit). Most of these patients (69.5%) had values below the average.

3.8.2 Alkaline phosphatase

Of the 195 patients included, 71 (36.5%) patients presented with normal ALP values, which range from 40 to 130 $^{UI}/_{l}$ (*Chart 9b*) at the Department of General Surgery of the Medical University of Graz. The arithmetic mean of ALP value of all the patients with measured values was 234 $^{UI}/_{l}$, meaning the majority (70.5%) of all patients with a measured ALP value presented with a value below and 44 (29.0%) with a value above this arithmetic mean, while one (0.5%) patient had exactly the average value.
The arithmetic mean of the patients with ALP values in the normal range is 85 $^{UI}/_{l}$. The minimum measured level of ALP was 43 $^{UI}/_{l}$ (42 $^{UI}/_{l}$ under and almost 2 times below average value), which was measured in 2 (1.0%) patients. The maximum level of ALP in patients with normal values was at 129 $^{UI}/_{l}$ (44 $^{UI}/_{l}$ above and more than 1.5 times above average value), which was as well measured in 2 (1.0%) patients. The exact average value was measured in 3 (4.0%) patients, while most of the other patients (55.0%) had values below the average.
The arithmetic mean of the patients with elevated ALP value is 374 $^{UI}/_{l}$. The minimum measured level of ALP in patients with elevated value was 132 $^{UI}/_{l}$ (242 $^{UI}/_{l}$ under and almost 3 times below average value), which was measured in 2 (1.0%) patients. The maximum value was at 2065 $^{UI}/_{l}$ (1691 $^{UI}/_{l}$ above and approximately 5.5 times above average value, but also almost 16 times more than the upper limit). Most of these patients (71.0%) had values below average.

3.8.3 Total bilirubin

Of the 195 patients included in the study, 104 (53.5%) patients presented with normal total bilirubin value, which is rated between 0.10-1.20 $^{mg}/_{dl}$ (*Chart 9c*) at the Department of General Surgery of the Medical University of Graz. The arithmetic mean of value of total bilirubin of all the patients with measured values was 3.01 $^{mg}/_{dl}$, meaning the majority (76.5%) of all patients with a measured total bilirubin level presented with a value below and 44 (23.5%) with a value above this arithmetic mean.
The arithmetic mean of the patients with total bilirubin values in the normal range is 0.56 $^{mg}/_{dl}$. The minimum measured level of total bilirubin was 0.15 $^{mg}/_{dl}$ (0.41 $^{mg}/_{dl}$ under and approximately 3.7 times below average value) and the maximum level of total bilirubin in

patients with normal value was at 1.18 $^{mg}/_{dl}$ (0.62 $^{mg}/_{dl}$ above and more than 2 times above average value), which was measured in 2 (1.0%) patients. Most of these patients (60.5%) had values below average.

The arithmetic mean of the patients with elevated total bilirubin value is 6.09 $^{mg}/_{dl}$. The minimum measured level of total bilirubin in patients with elevated value was 1.23 $^{mg}/_{dl}$ (4.86 $^{mg}/_{dl}$ under and almost 5 times below average value) and the maximum was at 38.00 $^{mg}/_{dl}$ (31.91 ^{mg}/dl above and approximately 6.2 times above average value, but also almost 32 times above average value). Most of these patients (67.5%) had values below average.

3.9 Coherency of elevated inflammation parameters

Of the 195 patients included, it was not possible to obtain one or both inflammation markers of 22 (11.5%) patients *(Chart 10)*.

Almost half of the patients (47.5%) did not have elevated CRP or leukocyte values in the last laboratory blood test. Sixty-two (32.0%) patients had only higher CRP levels, while isolated leucocytosis was seen in 4 (2.0%) patients.

Combination of both parameters being elevated was measured in 14 (7.0%) patients.

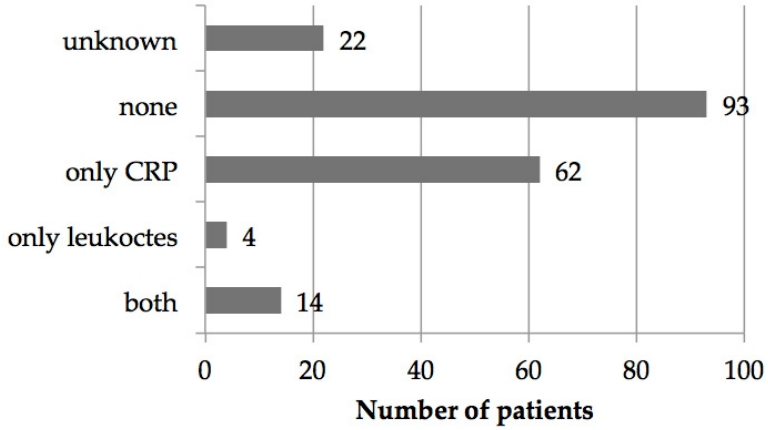

Chart 10: Coherency of elevated inflammation parameters.

3.10 Coherency of elevated cholestasis parameters

Of the 195 patients included, it was not possible to obtain at least one of the cholestasis parameters of 46 (23.5%) patients *(Chart 11)*.

Twenty-nine (15.0%) patients had all three parameters in the normal range. GGT was elevated in 35 (18.0%) patients, while isolated elevation of ALP was seen in only 1 (0.5%) patient and that of total bilirubin in only 3 (1.5%) patients.

A combination of elevated GGT and ALP parameters was measured in 22 (11.5%) patients, while 7 (3.5%) patients had a combination of higher GGT and total bilirubin and 2 (1.0%) patients had a combination of higher ALP and total bilirubin.

The largest share (25.5%) of the patients presented with all parameters elevated in the last laboratory test before the surgery.

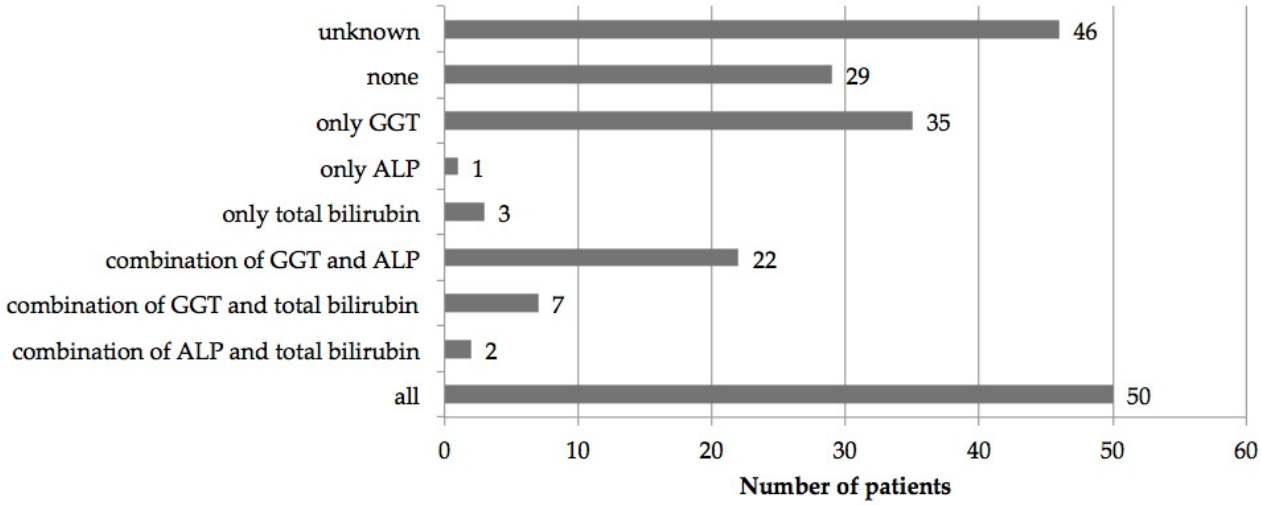

Chart 11: Coherency of elevated cholestasis parameters.

3.11 Coherency of elevated cholestasis and inflammation parameters

Of the 195 patients included, there were 29 (15.0%) patients with none of the cholestasis parameters elevated *(Chart 11)*. Most of the patients of this subgroup (72.5%) also had both inflammation parameters within the normal range *(Chart 12a)*. Six (20.5%) patients had only CRP values elevated and 2 (7.0%) patients presented with leucocytosis. There were no patients of this subgroup with both inflammation parameters elevated.

The second subgroup was composed of patients who had only GGT values above the normal range. Out of 35 patients, most of the patients (60.0%) had normal levels of the inflammation parameters, 11 (31.5%) patients presented with elevated CRP levels and 3 (8.5%) patients had elevated CRP as well as leukocytes levels *(Chart 12b)*. All patients with elevated leukocyte levels also had elevated levels of at least one of the other two inflammation parameters.

We were able to identify only one (0.5%) patient who only had the ALP value elevated *(Chart 11)*. This patient had no other parameters out of the normal range *(Chart 12c)*.

Out of 3 (1.5%) patients who had isolated total bilirubin elevation prior to the surgery *(Chart 11)*, 1 (0.5%) patient had leucocytosis, but the other 2 (1.0%) had no other elevated parameters *(Chart 12d)*.

Among different combinations of 2 elevated parameters out of 3, the largest share of patients (11.5%) tested with GGT and ALP levels above normal *(Chart 11)*. These 22 patients also had elevated CRP levels in 9 (41.0%) cases *(Chart 12e)*. One (4.5%) patient in this subgroup had both CRP and leukocyte levels elevated, but 12 (54.5%) patients had none of the inflammation parameters elevated.

Seven (3.5%) patients were included in the subgroup of elevated GGT and total bilirubin levels. For one (14.5%) patient it was impossible to obtain one of the inflammation

parameters (therefore listed as “unknown”). Of the rest, 4 (57.0%) patients had no other parameters above the normal levels, 1 (14.5%) presented with elevated CRP level and 1 (14.5%) with both inflammation parameters elevated *(Chart 12f)*.

Only 2 (1.0%) patients had only elevated ALP and total bilirubin levels *(Chart 11)*. One (50.0%) of these presented with no additional elevation in other observed parameters, while the other one (50.0%) had an elevated CRP level *(Chart 12g)*.

The last subgroup consisted of people with all 3 cholestasis parameters elevated. Eight (16.0%) patients were listed as “unknown” since we were unable to gain at least one of the inflammation parameters and were therefore unable to certainly define the right coherency between the observed data. Of the known data we were able to identify 12 (24.0%) patients with all 3 elevated cholestasis parameters who on the other hand had no inflammation parameters elevated *(Chart 12h)*. Almost half of the subgroup (48.0%) presented with additional elevation of CRP levels, while only additional leucocytosis was observed in only 1 (2.0%) patient. Both inflammation parameters were elevated in 5 (10.0%) patients.

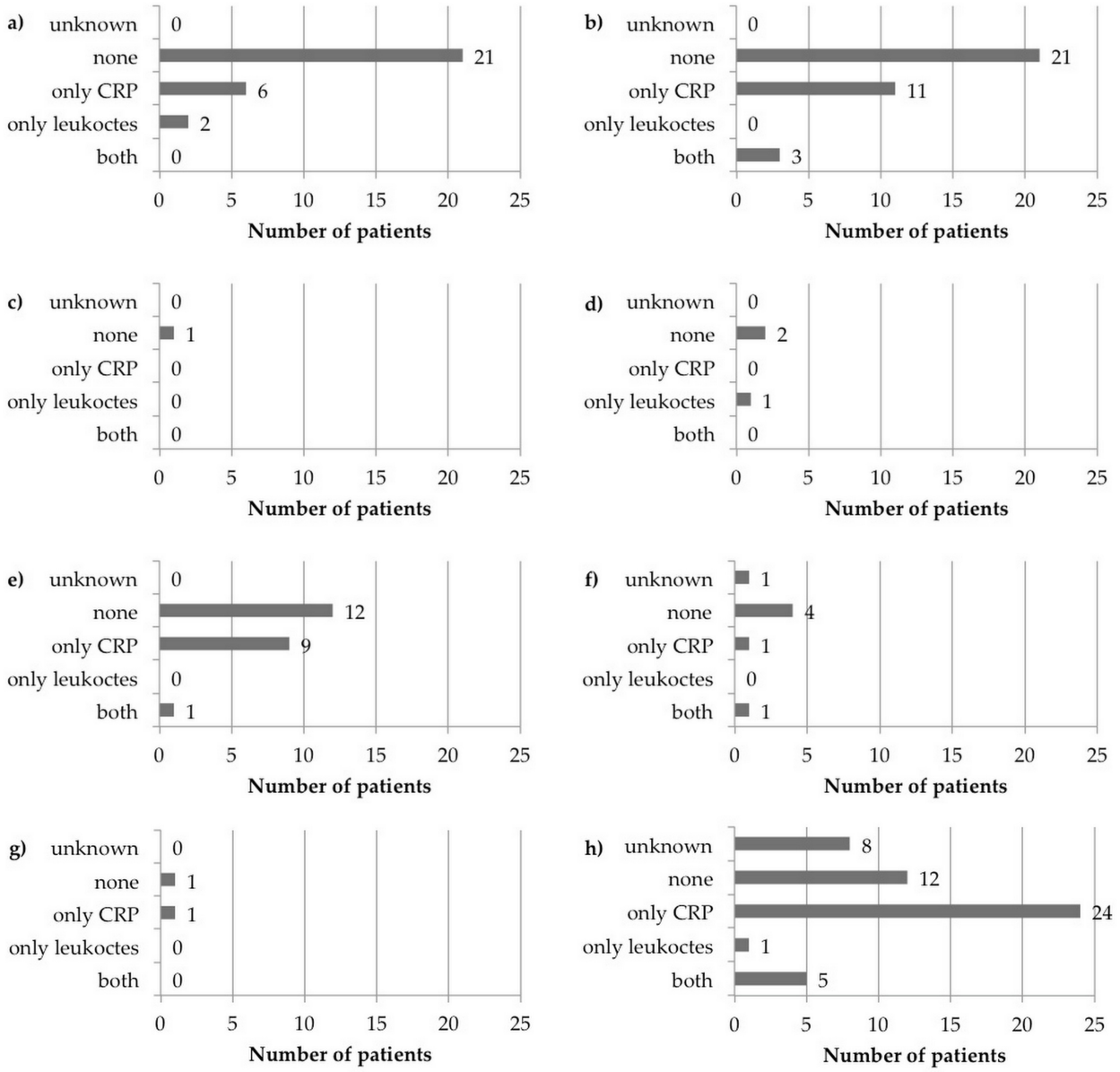

Chart 12: Elevated cholestasis parameters: (a) none, (b) gamma-glutamyltrasferase, (c) alkaline phosphatase, (d) total bilirubin, (e) combination of gamma-glutamyltrasferase and alkaline phosphatase, (f) combination of gamma-glutamyltrasferase and total bilirubin, (g) combination of alkaline phosphatase and total bilirubin, (h) all 3 parameters, and their coherency to elevated inflammation parameters.

4 Discussion

So far, scientific literature has not paid much attention to simultaneous inflammatory gallbladder changes in patients with pancreatic cancer and to the interdependence of these disease entities. Therefore, the purpose of our study was to determine the frequency of gallbladder changes in patients with pancreatic cancer and to analyse possible reasons.

Our study was based on a population of 195 patients with pancreatic cancer. Pathological changes of the gallbladder were seen in 156 of those patients, which represents 80%. Most of the patients (44%) presented with chronic cholecystitis, followed by 22% diagnosed with residues of previous cholecystitis. Chronic-active inflammation was observed in 11.5%, while acute inflammation was found in 1% and 2% had developed gallbladder malignancy; 5% presented with gallstones additionally to inflammation.

Zhang et al. retrospectively analysed gallbladders of 36 patients, who had surgical resection of a tumour in the head of the pancreas and had MR imaging performed within one month before surgery. The gallbladder was removed at the same surgery and analysed histopathologically. Histological gallbladder abnormalities were seen in 34 (94.5%) patients; all of them presented with chronic cholecystitis, 8 had additional cholelithiasis and 1 simultaneous acute cholecystitis. Two radiologists independently analysed the MR images and reported at least one gallbladder abnormality in 92% of the patients. The significant abnormalities were dilatation of cystic duct (67%), thickened gallbladder wall (58%), severe gallbladder wall enhancement (44%) and enlarged gallbladder (33%). The common bile duct was dilated in 64% and 19% presented with gallstones additionally to inflammation. While Zhang et al. analysed 36 patients and all of them had resectable tumours of the pancreatic head, in our study we included 195 patients with mixed localisations of the pancreatic tumour, resectable and unresectable. [30]

An important point of our study was to analyse the reasons for the high frequency of simultaneous cholecystitis in patients with pancreatic cancer:

One reason could be common risk factors, such as age, [31] obesity, [19,32–34] diabetes [19,35] or diet, [19,35,36] which can play a role in the development of pancreatic

cancer, but also of cholecystitis. In our study, the mean age of the patients at surgery was 64.1 years and 72.5% of the patients were older than 60 years. Overweight was a problem in 71 patients. Sixty-eight patients (35.0%) fit into the class of normal BMI and 2 patients were underweight, but it is impossible to state whether they had this low BMI already beforehand or it was a consequence of weight loss due to cancer.

Another reason for simultaneous occurrence of cholecystitis and pancreatic cancer is associated cholestasis. The chain of events starts with localisation of the tumour in the head of the pancreas. This growth may cause distal blockage of common bile duct, resulting in cholestasis and dilatation of common bile duct, followed by the cystic duct and afterwards by the gallbladder. Chronic cholestasis starts an inflammation process of the gallbladder. This is underlined by the MRI findings of Zhang et al., with twenty-four (67%) out of 36 patients with cancer of the pancreatic head having dilated common bile duct and cystic duct, enlarged gallbladder and/or chronic cholecystitis. [30]

We also analysed the frequent simultaneous occurrence of cholecystitis and pancreatic tumours in terms of tumour localisation and laboratory parameters:

As for tumour localisation, the most common origin of pancreatic tumours is the head of the pancreas. In our study, 87% patients were diagnosed with tumour lesions in the right side of the pancreas and 79% of them had changes in the gallbladder (including 4 patients, who had developed gallbladder malignancy) and cholestasis was present in 76% of them. If cholecystitis is present in patients with other tumour localisations, this may be explained with shared risk factors. One of these is diabetes, which is a possible risk factor for the emergence of pancreatic cancer as well as cholecystitis. In our study, 15 (7.5%) patients underwent surgery due to tumours in the left side of the pancreas, of which 14 patients had cholecystitis, but only 5 patients had cholestasis. Mostly the changes of the gallbladder in these patients were histologically described as minor.

As for the laboratory values, our analysis of cholestasis (GGT, ALP, total bilirubin) and inflammation (CRP, leukocyte count) parameters, in combination with possible presence of cholecystitis, resulted in 4 categories:

The first group represents patients with cholecystitis and elevated cholestasis as well as inflammation parameters. Here the reason may be the localisation of the tumour in the head of the pancreas. Growth of the tumour in the pancreatic head causes physical extrahepatic obstruction of bile flow due to compression of the bile duct and consequently results in dilatation of bile ducts as well as gallbladder, cholestasis and subsequently inflammation of gallbladder leading to elevation of inflammation markers. [4,6,10,19,21] In our study we found 114 (58.5%) patients with cholecystitis and simultaneously elevated cholestasis and inflammation parameters.

The second group consists of patients with cholecystitis, elevated inflammation parameters and normal cholestasis parameters. In these patients the simultaneous presence of pancreatic cancer and cholecystitis may be explained by shared risk factors such as adiposity [4,37] and diabetes [21,35,36,38] and by a weakened immune system. Our study identified 38 (19.5%) patients that fit into this particular group.

In the third group, the patients did not have cholecystitis but the cholestasis and inflammation parameters were elevated. A possible explanation for these changes is cholangitis. Our study identified 26 (13.5%) patients of this group.

Patients with elevated inflammation parameters, normal cholestasis parameters and no diagnosis of cholecystitis formed the last group. These changes could be due to other infections, e.g. pneumonia favoured by a weakened immune system and/or underlying risk factors of pancreatic cancer (for example, diabetes), which lead to increased susceptibility to infective agents. [6,32,35,39] In our study, 17 (8.5%) patients with no cholecystitis, normal cholestasis parameters and elevated inflammation parameters were found.

Cholecystitis, elevated cholestasis and inflammation parameters may hint at the possibility of pancreatic cancer, although they are no specific tools for its early diagnosis. Cholestasis and the previously described consequences are rather late symptoms of pancreatic cancer. An exception would be a tumour localisation in or close to the major duodenal papilla, which blocks bile drainage at an early stage. Additionally, all the analysed parameters, especially inflammation parameters, are too unspecific to determine pancreatic changes, as they can be elevated for numerous other reasons.

5 Conclusion

In summary, we have shown that in patients with pancreatic carcinoma, cholecystitis is very common. Most of our patients developed inflammation of the gallbladder due to the localisation of the tumour in the pancreatic head and extrahepatic obstruction of bile drainage, which triggered inflammation. In patients with other tumour localisations, cholecystitis may occur due to common risk factors (shared by pancreatic cancer and cholecystitis), such as adiposity and/or diabetes. Analysis of cholestasis and inflammation parameters in combination with possible presence of cholecystitis led to 4 different categories: In patients with cholecystitis and elevated cholestasis as well as inflammation parameters, cholecystitis is usually due to tumours in the pancreatic head and extrahepatic obstruction of bile drainage. Patients with cholecystitis, elevated inflammation parameters and normal cholestasis parameters may suffer from cholecystitis due to risk factors shared by cholecystitis and pancreatic cancer, such as adiposity and/or diabetes. Elevation of cholestasis and inflammation parameters in absence of cholecystitis may occur due to cholangitis and elevated inflammation parameters with normal cholestasis parameters and without cholecystitis may be attributed to other infections, e.g. pneumonia, favoured by a weakened immune system and/or underlying risk factors of pancreatic cancer (for example diabetes) leading to increased susceptibility to infective agents.
Cholecystitis, elevated cholestasis and inflammation parameters are usually rather late symptoms of pancreatic cancer. Although they are no specific tools for its early detection, they may be important hints leading to its diagnosis.

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Other language(s)

Self-assessment	Understanding				Speaking				Writing	
European level (*)	Listening		Reading		Spoken interaction		Spoken production			
English	C1	Proficient user	C1	Proficient user	C1	Proficient user	C1	Proficient user	C1	Proficient user
German	C1	Proficient user	C1	Proficient user	C1	Proficient user	C1	Proficient user	C1	Proficient user
Norwegian	B2	Independent user	B2	Independent user	B1	Independent user	B1	Independent user	B1	Independent user
Italian	B2	Independent user	B2	Independent user	B1	Independent user	B1	Independent user	B1	Independent user

(*) Common European Framework of Reference for Languages