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Single center experience in pancreatic neuroendocrine tumors

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Abbreviations

AJCC	American Joint Cancer Committee
CgA	Chromogranin A
CI	confidence interval
CT	computed tomography
ENETS	European Neuroendocrine Tumor Society
EUS	endoscopic ultrasonography
FNA	fine-needle aspiration
f-pNET	functional pancreatic neuroendocrine tumor
ISGPS	International Study Group of Pancreatic Surgery
MEN-1	Multiple Endocrine Neoplasia-type 1
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NF-1	Neurofibromatosis type 1
nf-pNET	non-functional pancreatic neuroendocrine tumor
PET	positron-emission tomographic
PFS	progression-free survival
pNET	pancreatic neuroendocrine tumor
PPI	proton pump inhibitor
PPPD	pylorus-preserving pancreaticoduodenectomy
RFA	radio frequency ablation
SIRT	selective internal radiation therapy
SPECT	single-photon emission computed tomography
SRS	somatostatin receptor scanning
sst	somatostatin receptor subtype
TACE	transarterial chemoembolization
TNM	tumor-node-metastasis
UICC	Union for International Cancer Control

VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel-Lindau disease
VIP	vasoactive intestinal peptide
WHO	World Health Organization
ZES	Zollinger-Ellison syndrome

1 Introduction

1.1 Nomenclature

Neuroendocrine tumors can arise from neuroendocrine cells throughout the body. Some of the tumors are able to produce peptides and hormones and cause characteristic symptoms (i.e. hypoglycemia, watery diarrhea). Others lack characteristic symptoms and get clinically apparent due to tumor mass effects (i.e. jaundice, abdominal pain, pancreatitis) [1]. In 1907 the German pathologist Siegfried Oberndorfer, who called them carcinoids, described these tumors for the first time [2]. Many years later the World Health Organization (WHO) introduced the term “neuroendocrine neoplasm” to accentuate the potential malignant behavior [3].

In 2006, the European Neuroendocrine Tumor Society (ENETS) introduced its own grading system [4]. The nuclear mitosis rate and the Ki-67 index are important components in the ENETS classification and in 2012 the first revision of the ENETS guidelines was published [5, 6].

Besides the efforts of the ENETS, the International Union for Cancer Control (UICC) also released a TNM staging system, which is accompanied by both the American Joint Cancer Committee (AJCC) and the WHO [7-9]. Due to the fact, that the UICC/AJCC/WHO 2010 TNM is the same as for ductal adenocarcinoma, it was adapted and validated recently [10]. The differences of the two systems will be highlighted in the following sections.

1.2 Epidemiology

pNETs are a diverse group of rare neoplasms and divided into two main groups, functional (f-pNET) and non-functional tumors (nf-pNET). The annual pNET incidence is 0,3 – 0,4 per 100 000 in the United States [11], 1,01 per 100 000 in Japan [12]. Interestingly, autopsy studies reported on an incidence of 10 % [13]. Beyond controversy the incidence has risen in the past decades, which might be due to a true change in disease or better disease detection.

nf-pNETs are twice as frequent as f-pNETs [14]. Data about functional pNETs vary in different publications, but the results indicate that insulinomas are the most frequent f-pNETs, followed by gastrinomas, glucagonomas, VIPomas, somatostatinomas and others [15, 16].

Most pNETs are sporadic, although, there are four inherited disorders, which are associated with a high incidence of pNETs in younger patients. The most common of these four is called Multiple Endocrine Neoplasia-type 1 (MEN-1). Patients suffering from MEN-1 will develop in 80 – 100 % nf-pNETs, in 50 – 60 % gastrinomas, in 20 % insulinomas and in 3 – 5 %

VIPomas or glucagonomas [17, 18]. Death at younger ages in MEN-1 patients is often because of pNETs [19]. Moreover, it is reported that the MEN-1 population account for 20 – 25 % of all gastrinomas, for 4 % of all insulinomas and for almost 8 % of all nf-pNETs [17, 20, 21].

Furthermore, there is von Hippel-Lindau disease (VHL), which is associated with a broad spectrum of pancreatic lesions. These patients mainly develop true pancreatic cysts (91 %), whereas a minority of 10 – 17 % has pNETs (primarily nf-pNET) [22].

Patients suffering from Neurofibromatosis type 1 (NF-1) (von Recklingshausen's disease) show in up to 10 % pNETs, whereas pNETs are even more infrequent in tuberous sclerosis patients (< 1 %) [18].

1.3 Pathogenesis

pNETs arise from neuroendocrine cells with both neural and endocrine characteristics. Historically it was believed that pNETs originate from the islets of Langerhans, but more recent studies revealed that pluripotent stem cells give rise to pNETs [23]. Hence, these tumors secrete typical substances, such as pancreatic polypeptide, Chromogranin A, synaptophysin or neuronspecific enolase [24, 25]. The sequence from a regular stem cell to a neuroendocrine tumor is still not understood. Nevertheless, specific gene mutations are frequently detected in pNET (*MEN1, DAXX, ATRX* and mTOR) [26]. Although, an alteration in most common oncogenes (fos, jun, myc, k-ras) or tumor suppressor genes (p53, retinoblastoma) is not often detected [27, 28].

1.4 Diagnosis

The diagnosis of f-pNETs is confirmed as a result of symptoms caused by the secreted hormones and subsequent biochemical testing. Nevertheless imaging studies are essential to distinguish primary tumor localization and the extent of disease to define if curative resection is possible or just cytoreductive surgery. pNETs are typically hypervascularized and therefore visualized in the early arterial phase of imaging. Moreover, imaging is indispensable to monitor patients after antitumor treatment. Biomarker profiles for patients suffering from a pNET are not as valid as for other solid tumors.

1.4.1 Conventional cross-sectional imaging

Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) are available in almost every clinic and as a consequence generally used to detect a pNET. ENETS demands a contrast-enhanced multidetector CT scan with slices < 1 mm at specified time points (arterial, portal-venous and late venous phase) [5]. Dependent on tumor size a sensitivity and specificity of a CT scan of 73 and 96 % is reached [29].

Since next generation contrast mediums and better MRI detectors are available this modality is also widely used. The tumors are well visualized in fat-suppressed T1-weighted images and combined with T2-weighted images a more subtle differentiation of the pancreatic tumor is feasible. MRI is mainly utilized for the detection and further distinction of liver tumors.

Taken together CT and MRI reach a sensitivity of 55 – 78 % for detecting the primary pancreatic tumor, however, are highly sensitive (94%) in tracing liver metastases. CT and MRI especially lose ground if the primary pancreatic tumor is smaller than 1 cm [30].

1.4.2 Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) is commonly used especially for very small tumors (< 1 cm). Moreover EUS can be combined with fine-needle aspiration (FNA) to distinguish between a nf-pNET and an adenocarcinoma or some other pancreatic tumor mass. In MEN-1 patients EUS plays an important role in identifying small pNETs since these patients suffer from nf-pNETs in 80 – 100 % [31]. EUS/FNA is rarely needed in f-pNETs because they are diagnosed by biochemical testing. A domain for EUS is the localization of small insulinomas, which are very small, intrapancreatic and not seen with conventional imaging methods and scintigraphy [32, 33].

However, EUS/FNA is highly operator-dependent, cannot accurately identify liver metastases and is more effective in localizing intrapancreatic than extrapancreatic masses, such as duodenal gastrinomas [34, 35].

1.4.3 Nuclear imaging

pNETs frequently (> 80 %) show high density of somatostatin receptor subtypes (sst), particularly sst 2 and sst 5 [36]. These receptors have a high affinity for synthetic somatostatin analogues, like octreotide and lanreotide, whereupon only octreotide is approved for patient use in the United States and is worldwide the most common applied agent for somatostatin receptor scanning (SRS or Octreoscan). For SRS radiolabeled octreotide (^{111}-In-DTPA-

octreotide) is used to detect pNETs and SRS is capable to identify 50 – 70 % of primary pNETs, although less than 25 % of insulinomas will be found because these tumors express only few sst 2 and sst 5 [37, 38]. This might also be due to the fact that insulinomas are often small and the sensitivity to identify tumors < 1 cm averages only 50 % [39]. SRS facilitates entire body scans and as a consequence distant metastases (i.e. liver, bone, lung) are identified quickly. Hence, studies have proven that the therapy strategy of patients with pNETs has changed because of SRS findings in 24 – 47 %. When SRS is combined with CT a sensitivity of 90 % and a specifity of 80 % is reached [39, 40]. False positive results occur in up to 12 % of patients mainly because of thyroid disease, breast disease, lymphoma or cholangiocarcinoma, nonetheless this rate can be minimized to 3 % if the findings are interpreted accurately within the clinical context [17, 40].

To detect pNETs positron-emission tomographic (PET) scanning was also tested, but this imaging method achieved inferior results. Responsible for this circumstance is the fact that pNETs have a slow glucose turnover [36]. The contemporary standard of SRS imaging represents the fusion of SRS with single-photon emission computed tomography (SPECT) and is available at almost every center.

“Next generation” in pNET-imaging represents ^{68}Gallium-DOTA-[Tyr3]octreotide (Ga-DOTA-TATE)-PET or ^{68}Gallium-DOTA-[Tyr3]octreotide (Ga-DOTA-TOC)-PET, however, these methods are available only in selected centers. With this scanning method, which features complete staging with one examination, the sensitivity is increased up to 97 % and an accuracy of 96 % is reached [41].

1.4.4 Biochemical assessment and functional localization

Since functional pNETs secrete a specific hormone, this hormone should be measured to establish the diagnosis. For insulinoma, it is recommended to assess serum levels of glucose, insulin, proinsulin and C-peptide during a fast [42].

On the other hand the majority of pNETs are non functional and not associated with a clinical hormone syndrome. Nevertheless, nf-pNETs secrete measurable levels of amines and peptides.

Chromogranin A (CgA) is the most commonly secreted, by both f-pNET and nf-pNET, and assessed protein. Tumor mass and secretory activity alter serum levels of CgA and it is thought that CgA correlates with tumor burden. Although, various non-malignant diseases also induce elevated serum levels of CgA, such as renal insufficiency, Parkinson’s disease, liver disease, pregnancy, and in patients taking proton pump inhibitors (PPI) CgA levels are also increased [43]. Contrarily, CgA levels may decrease during a therapy with somatostatin

analogs [44]. The sensitivity varies between 60 – 100 %, with a better sensitivity in metastatic disease than in patients with localized tumors [43, 45]. In patients taking consistent doses of somatostatin analogs a rise of CgA levels is highly suspicious for tumor growth and/or loss of secretory control [46, 47]. Taken together screening or testing with CgA for pNET is not recommended.

A biomarker panel consisting of CgA and pancreatic polypeptide increases the sensitivity for diagnosis of nf-pNET to 94 % [48].

In recent years the approach of functional localization of pNETs by assessment of hormone concentrations in the portal blood has disappeared almost completely from clinical routine. This technique was used to establish the diagnosis of an insulinoma, which was not seen with conventional imaging methods. The original portal-venous-sampling was replaced subsequently by selective-arterial injection of secretin (to detect gastrinomas) or calcium (to detect other pNETs) combined with angiography. Selective intra-arterial injection of calcium in combination with hepatic venous insulin sampling is proven to be a sensitive (88 – 100 %) diagnostic tool to localize insulinomas [49, 50].

Since, imaging modalities has improved there is almost no indication left for these special kinds of examination. Nowadays it is occasionally applied in patients with insulinomas or gastrinomas not localized by other diagnostic methods [49, 51].

1.5 Functional pancreatic neuroendocrine tumors

1.5.1 Insulinoma

This entity is the most common functional pancreatic neuroendocrine tumor, presenting with autonomous insulin production. An estimated incidence of 1 – 3 per million population per year is reported [17, 52]. Insulinomas are usually benign (85 – 95 %), single tumors and become clinically apparent with Whipple's Triad, although, there is a delay in diagnosis on average of four years [53]. The classical clinical signs are symptoms of hypoglycemia, high insulin levels with plasma glucose levels < 50 mg/dl and relief of symptoms after administration of glucose (Whipple's Triad) [54]. Furthermore, insulinomas cause neuroglycopenic symptoms, such as confusion, visual changes and coma, or as well symptoms due to hypoglycemia, such as weakness, sweating and tachycardia. Due to these various symptoms a significant number of patients is initially admitted to psychiatry. Typically patients develop symptoms after fasting or exercising. Drawing conclusions from the severity of the symptoms on the tumor burden is not possible [55, 56].

The gold standard for diagnosing an insulinoma is supervised fasting for 72 hours with documentation of glucose and insulin blood levels. About 30 % of patients have ailment within 12 hours, 80 % at 24 hours, 90 % at 48 hours and 100 % at 72 hours [53]. To rule out insulin misuse the blood levels of C peptide and/or proinsulin should be measured. If these levels are increased the diagnosis of Insulinoma is established [57]. Insulinomas may be a part of MEN-1, in which case the tumors are almost always multiple and difficult to diagnose.

After the endogenous hyperinsulinism is proven the tumor mass has to be assessed. As mentioned above, there are plenty of imaging modalities to determine the dimension of the disease. Genetic testing should also be done to rule out MEN-1, as therapy strategy differs substantially between MEN-1 and a sporadic insulinoma.

1.5.2 Gastrinoma

Gastrinomas ectopically secrete gastrin, which leads to Zollinger-Ellison syndrome (ZES). ZES is characterized by peptic ulcer disease (stomach and duodenum), abdominal pain, secretory diarrhea and gastroesophageal reflux disease. Similar to insulinoma there is a delay in establishing the diagnosis of a gastrinoma of about six years. Gastrinomas are malignant in 60 – 90 % of cases, usually small (< 1 cm) and in 60 % gastrinomas are found in the duodenal wall in patients with sporadic ZES. This rate increases up to 85 % in patients with MEN-1/ZES, moreover, these patients always develop multiple tumors [17, 52, 58-60].

If ZES is suspected fasting gastrin level has to be measured and PPIs need to be ceased seven days prior to the blood test. Additionally, a gastroscopy has to be done to take biopsies and measure gastric pH. The diagnosis is verified when serum gastrin is > 1000 pg/ml, gastric pH is < 2 and biopsies lack to prove atrophic gastritis. If gastrin is moderately elevated (100 – 1000 pg/ml) a secretin test is required because gastrinomas ectopically express secretin receptors. Intravenous administration of secretin provokes increased secretin secretion by the gastrinoma. An accentuation of secretin blood level of > 120 pg/ml is argumentative for a gastrinoma with a sensitivity of 94 % and a specifity of 100 %, if the patient is not taking PPIs [58, 61, 62].

Recent studies indicate that the widespread use of PPIs may mask the symptoms of ZES and therefore delay the diagnosis. This is because PPIs, in contrast to H2-receptor antagonists, attenuate the symptoms of acid hypersecretion in most ZES patients. Moreover, PPIs lead to elevated gastrin levels in non-ZES patients. PPI treatment may lead to 60 % of gastrin levels of ZES patients [61, 63].

Another problem in detecting ZES in MEN-1 patients may be due to hypercalcemia after sufficient treatment of hyperparathyroidism. Hypercalcemia influence fasting gastrin levels,

basal acid output and the secretin test hence hinder the diagnosis [64].

1.5.3 Glucagonoma

The eponymous secreted hormone of this tumor is glucagon, which causes glucose intolerance (40 – 90 %), weight loss (80 %) and a pathognomonic rash, called migratory necrolytic erythema (70 – 90 %). This neoplasia is commonly malignant, large at diagnosis (mean 6 cm) and in more than 60 % liver metastases are apparent [65, 66].

Clinically significant hyperglycemia occurs in only half of the patients. The migratory necrolytic erythema is caused by direct glucagon infusion and leads in some cases to the diagnosis – made by a dermatologist. Raised erythematous patches beginning in the perineum and progressing to the trunk and the extremities characterize this rash. However, the rash is not characteristic for glucagonoma, since it also occurs in celiac disease, cirrhosis and pancreatitis [67].

To establish the diagnosis of a glucagonoma extraordinary elevated glucagon serum levels have to be demonstrated (500 – 1000 pg/ml) in a patient [65].

1.5.4 VIPoma

Verner and Morrisson first described the typical symptoms of this disease in 1958 (Verner-Morrisson syndrome) [68], which are diagnostic. These symptoms include watery diarrhea, (> 700 ml/d in 100 %, > 3000 ml/d in 70 – 80 %), hypokalemia (70 – 100 %) and hypochlorhydria (35 – 76 %). The large volume diarrhea often leads to dehydration and electrolyte disturbances, a metabolic acidosis is also seen due to the fecal loss of bicarbonate. At presentation the tumors are metastatic in 70 – 80 % of patients, however VIPomas are usually single tumors. To secure diagnosis measurement of elevated serum VIP level (> 500 pg/ml) in combination with high volume diarrhea is required [69-71].

1.5.5 Somatostatinoma

Somatostatinomas are the least common of the five well-described f-pNETs. These tumors are usually single tumors, either found in the duodenum (50 %) or in the pancreas (50 %) and half is malignant. The classical symptoms accompany a somatostatinoma are diabetes mellitus, gallbladder disease, weight loss, diarrhea, steatorrhea and anemia. Because of the unspecific symptoms the diagnosis of a somatostatinoma is even later confirmed. There is no reliable provocative test to detect a somatostatinoma. To confirm the diagnosis a pancreatic

tumor combined with typical symptoms and elevated serum levels of somatostatin are recommended [65, 72, 73].

Tumor	Symptoms or signs	Incidence of metastases	Extrapancreatic location
Insulinoma	Hypoglycemia resulting in intermittent confusion, sweating, weakness, nausea; loss of consciousness may occur in severe cases	<15%	Rare
Glucagonoma	Rash (necrotizing migratory erythema), cachexia, diabetes, deep venous thrombosis	Majority	Rare
VIPoma, Verner-Morrison Syndrome, WDHA Syndrome	Profound secretory diarrhea, electrolyte disturbances	Majority	10%
Gastrinoma, Zollinger-Ellison Syndrome	Acid hypersecretion resulting in refractory peptic ulcer disease, abdominal pain, and diarrhea	<50%	Frequently in duodenum
Somatostatinoma	Diabetes, diarrhea, cholelithiasis	Majority	Rare
Non-functioning	May be first diagnosed due to mass effect	Majority	Rare

WDHA: Watery Diarrhea, Hypokalemia and Achlorhydria.

Fig. 1. Clinical presentation of the different pNETs [74]

1.6 Classification

1.6.1 Evolution of classification systems

Since Oberndorfer [2] first mentioned carcinoids over 100 years ago there were different attempts to categorize these tumors. In 1980, the WHO used the term carcinoid for every tumor of the neuroendocrine system, “excluding pancreatic endocrine tumour [sic!] (islet cell tumour [sic!]), medullary carcinoma of the thyroid, paraganglioma, small cell lung carcinoma and Merkel cell tumour [sic!] of the skin” [75]. This classification subdivided the tumors on the basis of different staining methods but failed to estimate patient outcome. Besides the ambiguous term carcinoid the medical society used inaccurate descriptions such as local, locally advanced and metastatic.

Capella et al. published a landmark study in which they introduced the term “neuroendocrine tumor” instead of carcinoid, which implies the whole neuroendocrine tumor entity. Moreover, this working group proposed further statements to finally establish guidelines for the clinician. Their classification subdivided the tumors into tumors with benign behavior, uncertain behavior and into low malignancies, resulting in highly malignant neoplasms (Figure 2) [75].

Table 2 Neuroendocrine tumours of the pancreas

Benign	
Functioning well-differentiated non-angioinvasive tumour of small size	
insulinoma	(size <2 cm)
others[b]	(size <1 cm)
Nonfunctioning well-differentiated non-angioinvasive tumour of small size	(<2 cm)
Benign or low-grade malignant	
Functioning well-differentiated non-angioinvasive tumour of intermediate size	
insulinoma	(size 2–3 cm)
others[b]	(size 1–2 cm)
Nonfunctioning well-differentiated non-angioinvasive tumour of intermediate size (2–3 cm)	
Low-grade malignant[a]	
Functioning well-differentiated tumour of large size and/or with angioinvasion	
insulinoma	(size >3 cm)
others[b]	(size >2 cm)
Nonfunctioning well-differentiated tumour of large size (>3 cm) and/or with angioinvasion	
High-grade malignant	
Functioning or nonfunctioning poorly differentiated intermediate or small cell carcinoma	

[a] If metastases or gross invasion are present, tumour should be called low-grade neuroendocrine carcinoma
[b] Other functioning tumours: gastrinoma, vipoma, glucagonoma, serotonin producing tumour, others

Fig. 2. Scheme of the different neuroendocrine tumors postulated in 1995 by Capella et al. [75]

Based on this work the WHO published in 2000 a classification for gastroenteropancreatic neuroendocrine tumors. This classification adopted the idea to subdivide the tumors by their dignity and therefore distinguish between well-differentiated tumors (with benign and uncertain behavior), well-differentiated neuroendocrine carcinomas and poorly differentiated carcinomas [76]. The prognostic value of this classification system has been proved in several studies [15, 77, 78].

Nonetheless, this classification system failed to be adopted into clinical routine, thus in 2006 a consensus proposal including a grading system was published. From this proposal evolved the ENETS their guidelines for neuroendocrine tumors, including pNETs, published in the same year and adapted in 2012. The ENETS guidelines refer to the tumor-node-metastasis (TNM) system in combination with a grading classification based on the mitotic rate and/or Ki-67 proliferation index [4 5, 6].

In 2009 the AJCC presented the 7th edition of the AJCC manual and for the first time the manual contained a staging classification for neuroendocrine tumors [8]. Unfortunately, the TNM staging for pNET is derived from exocrine pancreatic adenocarcinoma.

In 2002 another classification system was published, which is called Hochwald classification system [79]. This classification system focuses on well-differentiated pNETs and a recent study even showed its superiority to ENETS and AJCC guidelines in this subdomain when it is combined with proliferation Ki-67 index [79].

Moreover, the North American Neuroendocrine Tumor Society (NANETS) also developed guidelines. These guidelines were published in 2010 and concern both clinical management and histopathological diagnostics of pNETs [80, 81].

The ENETS and the AJCC staging system are worldwide in use, however, differ in several significant points, which will be highlighted in the next sections. Due to the discrepancies of the two main staging systems awareness has risen that this will lead to disarrangement in clinical routine and hinder scientific communication [82].

1.6.2 ENETS guidelines

The ENETS guidelines are based on the published experience of single centers and were devised at the first ENETS Consensus Conference in November 2005. Since then the guidelines were confirmed at least in seven autonomous surveys [83-89] and were revised at the second ENETS Consensus Conference in 2012 and published subsequently [5, 6].

The classification system is based on a 4-stage TNM classification combined with a grading classification (low, intermediate, high). From ENETS standpoint in 2005 there was no grading system that accurately predicted the behavior of well-differentiated endocrine tumors. Hence, the society decided to incorporate a grading classification into their guidelines. The grading classification was established referring to the contemporary WHO criteria. The three tumor categories are discriminated due to their proliferation status determined by mitotic count and/or Ki-67 index (Figure 3) [4].

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

[a]10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density
[b]MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

Fig. 3. The grading system for pNETs, published by ENETS [4]

Although the grading of the tumor is important there are groups who want to adapt the grading scores. In a study the proliferation index was evaluated and the authors suggest determining new cut-off levels for Ki-67. They reached prognostic stratification within the

groups not before they set the cut-off at 5 – 20 % [87].

The ENETS guidelines, as other TNM classifications, postulate four stage classes (I – IV), whereat stage II and III are subdivided into IIA, IIB and IIIA and IIIB, respectively. Recently, it was demonstrated that death risk ascend statistically significant from stage I to stage IV [89].

Another working group published a retrospective study purporting survival rates at 5 years after foregut NET (stomach, duodenum, pancreas). The survival rates for stage I was 100 %, for stage II 89,5 %, for stage III 79,1 % and for stage IV 55,4 %. However, there was only statistical significance between stage I vs. IV, whereas the difference between stage I vs. II and stage II vs. III was not significant. As mentioned above, this study included NETs of the stomach, the duodenum and the pancreas [86].

1.6.3 AJCC guidelines

In 2007 Bilimoria et al. published a study to prove the prognostic value of the AJCC TNM manual (6th edition) for pancreatic adenocarcinoma for pNETs. The authors identified patients from the National Cancer Data Base (1985 – 2004) to test their hypothesis. After evaluation of their data, they postulated "the staging system can effectively stratify patients with pNETs" and "provides survival discrimination by stage for surgical and nonsurgical patients" [90]. It was not until 2010 that the AJCC guidelines for pNETs were published [8] and may be built on these findings. Unfortunately the guidelines for pNETs were derived from those for exocrine adenocarcinoma. In contrast to the ENETS guidelines the AJCC classification is based on a cancer registry database publication and up to now was validated only once. This study concluded that "the AJCC TNM classification is prognostic for overall survival and can be adopted in clinical practice". Nonetheless the survival comparison between stages I vs. II and II vs. III were not statistically significant, although the difference between stages I vs. IV was significant [10]. The AJCC TNM manual distinguishes between localized (stage I), locally advanced resectable (stage II), locally advanced unresectable (stage III) and distantly metastasized tumors (stage IV).

The two main guidelines differ in the definitions of T stages, obviously mainly in T2 and T3 and it is reported that this difference can affect the prognostic value. The 10 year prognosis in patients with ENETS stage I tumors is 96 % in contrast to patients suffering from AJCC stage I tumors (71 %). It is supposed that this is caused by the inclusion of ENETS stage II tumors in AJCC stage I [87, 91].

Another main distinction is the AJCC recommendation to record the tumor grade but the manual lacks a specific guideline for grade assignment.

Definitions of TNM				**Proposal for a TNM Classification and Disease Staging for Endocrine Tumors**			
Primary Tumor (T)				**T—Primary Tumor**			
TX	Primary tumor cannot be assessed			TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor			T0	No evidence of primary tumor		
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension			T1	Tumor limited to the pancreas and size <2 cm		
T2	Tumor limited to the pancreas, >2 cm in greatest dimension			T2	Tumor limited to the pancreas and size 2–4 cm		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery			T3	Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)			T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)		
				Note: For any T, add (m) for multiple tumors			
Regional Lymph Nodes (N)				**N—Regional Lymph Nodes**			
NX	Regional lymph node(s) cannot be assessed			NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis			N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis			N1	Regional lymph node metastasis		
Distant Metastasis (M)				**M—Distant Metastases**			
—				MX	Distant metastasis cannot be assessed		
M0	No distant metastasis			M0	No distant metastasis		
M1	Distant metastasis			M1a	Distant metastasis		
Endocrine and Exocrine Pancreas				**Endocrine Pancreas**			
Stage	T	N	M	Stage	T	N	M
0	T0	N0	M0	—	—	—	—
IA	T1	N0	M0	I	T1	N0	M0
IB	T2	N0	M0	—	—	—	—
IIA	T3	N0	M0	IIa	T2	N0	M0
IIB	T1	N1	M0	IIb	T3	N0	M0
	T2	N1	M0	—	—	—	—
	T3	N1	M0				
III	T4	Any N	M0	IIIa	T4	N0	M0
				IIIb	Any T	N1	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

Fig. 4. UICC (left) and ENETS (right) classification system [80]

1.7 Treatment

1.7.1 Surgery

Although, management of patients with pNET is achieved via a multidisciplinary evaluation and treatment, surgery is the only potentially curative strategy for these patients [11]. A retrospective study including 728 patients with pNET compared the survival times of patients who underwent surgery and those who did not. Patients whose tumor was resected had a mean survival of 60 months compared to 31 months in the non-operative group, which is statistically highly significant [92].

Furthermore, surgery can control hormone secretion and accompanied syndromes. Since it is known that PPI treatment is highly effective in ZES patients, however, gastric surgery is no longer indicated to reduce acid secretion in ZES patients.

When surgery is considered preoperative staging has to be completed and the tumor detected. Nonetheless, if the diagnostic tools fail to do so, explorative laparotomy can be performed to localize and resect the tumor. The literature demonstrates that an experienced surgeon mostly (> 95 % of insulinomas or gastrinomas) localize the pNET [59, 93]. Therefore blind pancreatectomy in the case of no detected tumor is not indicated. When surgical resection of a pNET is done it is recommended to perform an accurate exploration of the whole abdomen, followed by an intraoperative ultrasonography of the pancreas and in some cases duodenotomy is indicated. Intraoperative ultrasonography is also useful to identify the main pancreatic duct and therefore plan the resection. Duodenotomy is recommended for tumors with a predilection site for the duodenum such as gastrinomas or somatostatinomas [94].

If the tumor is small (< 2 cm) and expectably benign (i.e. insulinoma), a parenchyma sparing operation is indicated. As more than 90 % of insulinomas are benign enucleation has become the standard procedure. If the tumor is too big for enucleation a spleen-preserving distal pancreatectomy is generally preferred (Kimura's procedure) [95].

A laparoscopic approach for small benign tumors is well established, since the first successful series in 1996 [96]. Since then laparoscopic surgery is reserved for tumors located in the body or the tail, resected either by enucleation or by spleen-preserving distal pancreatectomy. It has been shown that laparoscopic pancreas surgery is a safe procedure and pancreatic fistulas are not more frequent than in open surgery [97]. Nonetheless, if there are signs of malignancy, such as local invasion or distant metastases, or pancreaticoduodenectomy is indicated conversion to open surgery is obligate.

A more radical operation is indicated if the tumor is potentially malignant or bigger than 2 cm or located in the head of the pancreas. The extent of lymphadenectomy required is still

controversial due to the fact that there is no correlation identified between lymph node metastases and overall survival [15, 98]. nf-pNETs often get clinical apparent due to mass effects and patients often suffer from distant metastases at diagnosis. Patients with such advanced disease should also be considered for surgery, although this is possible only in selected patients. Debulking surgery in these patients should target to resect at least > 90 % of the tumor burden, although hepatic recurrence is high, with up to 76 % of patients with recurrent metastases to the liver within two years [80, 99].

The surgical management in patients with hereditary syndromes differs to patients with sporadic pNETs. The timing and extent of surgery for nf-pNETs in patients with MEN-1 is still controversial. In patients with MEN-1 nf-pNETs are multifocal and local resection is not expected to result in cure. Nonetheless, there is consensus that nf-pNETs in MEN-1 patients bigger than 2 cm or tumors that cause symptoms should be resected. Smaller tumors are treated differentially in diverse centers. There are groups who propose surgery if the tumor size is 1 cm [100, 101]. ENETS recommends surgery for nf-pNETs at 2 cm [102]. If surgery has to be done for small, potentially benign nf-pNETs in MEN-1 patients, parenchyma sparing procedures are recommended because subsequent surgery is often necessary.

Inuslinomas in patients with MEN-1 are usually resected as described above [30]. The surgical management of MEN-1 ZES was controversial discussed recently [94]. Due to the fact that liver metastases will occur in 23 – 39 % in patients with MEN-1 ZES an aggressive approach is recommended. After pylorus-preserving pancreaticoduodenectomy (PPPD) the risk of distant liver metastases is declined to 3 – 5 % [103].

1.7.2 Symptomatic management

Insulinomas are treated surgically with excellent cure rates, however, symptom control has to be achieved prior to surgery and in patients with malignant disease. A first step to relieve symptoms is dietary modification with frequent small feedings. To control insulinoma induced hypoglycemia more reliable administration of diazoxide (200 – 600 mg/d) is used. Diazoxide is a benzothiazide and therapeutic success is achieved in 50 – 60 % of patients. Side effects, such as fluid retention (frequent), nausea and occasional hirsutism (at higher doses), may occur and require additional medication like diuretics [42, 53, 104]. Long-acting somatostatin analogs (octreotide, lanreotide) can also ease hypoglycemic symptoms in up to 50 %. However, they have to be used with caution, as they may worsen the hypoglycemia [38].

Gastrinomas ectopically secrete gastrin, which leads to ZES. By now PPIs are the gold standard agents to control the acid hypersecretion in almost every patient with ZES. H2-receptor antagonists and somatostatin analogs are also effective but frequently high doses

have to be administered. PPIs are taken once or twice a day in standard doses (i.e. 40 mg omeprazole). Higher doses are needed in patients with MEN-1 or severe gastroesophageal reflux or prior Billroth II resection. Data on long-term usage of PPIs in ZES patients demonstrates no evidence of tachyphylaxis and an excellent safety profile [58, 105, 106].

Other f-pNETs are treated with long-acting somatostatin analogs (octreotide, lanreotide), which is effective in the initial management of glucagonomas, VIPomas and in some somatostatinomas. Due to recent formulation of the drugs a monthly depot injection is sufficient which is a great advancement and leads to higher patient convenience. Octreotide can reduce serum VIP levels in patients with VIPoma in > 80 % and ease diarrhea in > 75 %, however this excellent response rates are short-lived without increase in the dosage. Adverse effects of somatostatin analogs are generally mild, including flatulence diarrhea/steatorrhea, nausea, gallstones, and glucose intolerance [102, 107, 108].

1.7.3 Liver directed therapy

As mentioned above, synchronous liver metastases should be treated surgically if > 90 % of the tumor burden can be removed [80, 99]. Repeated resection for resectable recurrent disease is favored and overall 5-year survival rates of 65 % can be achieved [100, 109].

If complete surgical resection of all liver metastases is not feasible, a combination of resection and ablation can be employed. Radio frequency ablation (RFA) can be used alone or in conjunction with cytoreductive surgery; if RFA is applied alone this is possible via a percutaneous or laparoscopic approach. Advantages of RFA are a low morbidity (< 15 %), high response rates (90 – 95 %), symptom relief is often achieved (> 95 %) and RFA can be repeated if necessary. Limiting factors for RFA are tumor location, size and number [110-112].

Patients with unresectable liver metastases can be treated with embolization methods to control hormone symptoms or as a palliative therapy. Liver metastases derive their blood supply basically from hepatic artery branches, hence they are targeted via transarterial embolization. The techniques of embolization range from bland embolization to embolization with chemotherapeutic agents or embolization with radionuclides. Transarterial chemoembolization (TACE) uses beads coupled with conventional chemotherapeutic agents (such as doxorubicin, cisplatin, streptozocin) and is typically repeated every 6 – 8 weeks. There are various studies, which report on a symptom relief in 50 – 100 % and a tumor shrinkage in 25 – 86 % [45, 113].

More recently, beads coupled to radionuclides are used to deliver ionizing radiation directly into the tumors. For internal radiotherapy administration of Yttrium-90 (Y-90) particles are used with promising results. A prospective study with 34 patients showed radiologic

response in 50 % including 18 % with complete response [114].

The side effects of embolization therapy are low, including pain, nausea and fever. Contraindications to TACE and other embolization procedures include liver dysfunction, portal venous thrombosis and history of biliary reconstruction [115].

1.7.4 Chemotherapy

1.7.4.1 Somatostatin receptor pathway

Somatostatin, physiologically produced in the brain, pancreas, stomach and intestine binds to G-protein-coupled somatostatin receptors and influences on cell growth and neurotransmission processes. There are 5 known somatostatin receptors subtypes: sst1, sst2, sst3, sst4 and sst5. Approximately > 80 % of pNETs express somatostatin receptors. Traditionally, somatostatin analogs are used in patients with large tumors and in patients suffering from hormone hypersecretion. A prospective study (PROMID) investigated the value of long-acting octreotide in patients with low-grade metastatic NET of the midgut. The study could demonstrate that treatment with octreotide could double the time to progression compared with placebo (14,3 months vs. 6 months) [116, 117]. A subsequent multi-center study, which used lanreotide (CLARINET), could prove these results. Their study population consisted of patients with metastatic disease with a Ki-67 index < 10 % and the progression-free survival could significantly be prolonged [118]. Nonetheless, no study could demonstrate so far how the anti-proliferative effects of the biotherapy were functioning.

1.7.4.2 Traditional chemotherapy

Different agents have been tested in patients with advanced pNETs and some efforts were made. The first agent with proven significant benefit was streptozocin, however, due to severe side effects this approach has been left [119]. Over time many different combinations of vrious agents were tried out, with most effects seen with streptozocin/doxorubicin, streptozocin/fluorouracil or streptozocin/doxorubicin/fluorouracil [120, 121]. The three-drug regimen was associated with an overall response rate of 39 % and median survival duration of 37 months [122].

1.7.4.3 mTOR pathway

The mammalian target of rapamycin (mTOR) is an intracellular serine-threonine kinases that influences cell growth, proliferation, metabolism and apoptosis and is upregulated in many cancer types. Temsirolimus and everolimus are rapamycin derivatives, which have been evaluated in clinical trials for the treatment of patients with pNETs. Temsirolimus reached an objective response rate of only 5,6 % in a phase II study of 37 patients. Hence further monotherapy studies with temsirolimus were not pursued [123].

Everolimus was initially evaluated in a study of 60 patients with neuroendocrine tumors of which 30 patients suffered from a pNET. In this study everolimus was combined with a long-acting release form of octreotide. The 30 patients with pNET showed an overall tumor response rate of 27 % and a progression-free survival (PFS) of 50 weeks [124].

Based on these findings a phase II clinical trial (RADIANT-1) was initiated. RADIANT-1 included 160 patients with metastatic pNETs receiving either everolimus as a single agent or everolimus combined with octreotide LAR. Median PFS was longer in the combination group (16,7 vs. 9,7 months) [125]. Subsequently, RADIANT-2 and RADIANT-3 were drafted and proved that everolimus, with or without octreotide LAR, prolong the median PFS compared to placebo, with or without octreotide LAR. The median PFS reached in RADIANT-2 was 16,4 vs. 11,3 months and in RADIANT-3 11 vs. 4,6 months. The side effects of everolimus treatment are mild, including stomatitis, rash, diarrhea and fatigue. [126, 127] Multiple trials investigating the use of everolimus in combination with other agents in patients with pNET are ongoing (www.clinicaltrials.gov).

1.7.4.4 VEGF pathway

Angiogenesis in tumor growth is a well-established phenomenon. Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis and the VEGF-family consists of 6 proteins interacting with 3 receptors (VEGFR-1, VEGFR-2, VEGFR-3). VEGFR-2 is thought to be the most important factor in tumor cell angiogenesis [128]. For clinical purpose there are agents available interfering directly with VEGF (bevacizumab) or block the receptor (sunitinib, sorafenib).

Bevacizumab is a monoclonal antibody that binds to circulating VEGF and has to be combined with a cytotoxic agent for most solid tumors. Combination therapy with bevacizumab in patients with pNETs has been undertaken. In one study Bevacizumab was combined with temozolomide including 18 patients with pNET. Four patients with pNET showed partial response [129]. In a more recent study 55 patients with pNETs were treated with a combination of temsirolimus and bevacizumab. The response rate in this study was 37 %. 49 patients were evaluated for PFS and in this population 49 % were progression-free at 12 months [130].

Sunitinib inhibits all 3 VEGFRs and some other tyrosine kinase receptors. In a first study efficacy of sunitinib was proven in patients with pNET showing a response rate of 16,7 % [131]. Based on these findings a phase III clinical trial was enrolled which should include 340 patients with well-differentiated pNETs. After analyzing the first 171 patients the ongoing study was discontinued due to an increased number of deaths in the placebo group. Patients in the verum group had a PFS of 11,4 months compared to 5,5 months in the placebo group. Reported side effects of sunitinib were neutropenia, hypertension and fatigue [132].

Sorafenib blocks VEGFR-2 and some other tyrosine kinase receptors, however, this agent has only moderate effects on pNETs. In a study with 43 patients suffering from metastatic pNET only 10 % had partial response and 6-month PFS was seen in 14 of 23 evaluable patients [133].

1.7.5 Liver transplantation

Liver transplantation was performed in patients with metastatic pNETs. The reported series of patients treated with liver transplantation for metastatic pNET are very small. According to the literature the optimal patient for liver transplantation is young (< 50 years), the tumor is not resectable and limited to the liver and shows a favorable histology with a low Ki-67 index and causes hormonal symptoms. Nonetheless the results for liver transplantation in patients with metastatic pNET are disappointing. In a recent review with 85 cases the overall 5-year survival was 45 % [134, 135].

2 Aim of the study

Pancreatic neuroendocrine tumors represent only 1 – 2 % of all pancreatic neoplasia.

Firstly, aim of this study was to identify patients who underwent a pancreatic resection because of a pNET between 1996 and 2011 at our institute.

Secondly, a detailed characterization of the patients was necessary to interpret prognostic factors.

Thirdly, the focus was on the prognostic value of pathologic diagnostic criteria as in ENETS and TNM staging guidelines.

Thirdly, the postoperative course and complication rate in the study population was analyzed and the impact of various factors on the morbidity should be analyzed.

Fourthly, the survival rates and their influencing factors should be evaluated.

3 Material and methods

3.1 Assessment

Between June 1996 and November 2011, 66 consecutive patients with a pancreatic neuroendocrine tumor were operated at our institute. All patients with histologically confirmed pNETs were included in this study. The tumor burden of these 66 patients was resected. Patients who just have undergone explorative laparotomy were excluded. Patient data were entered into a computerized database, and follow up was recorded for each patient available. Median follow up for all patients was 39,2 months. All data were analyzed with respect to demographic data (patient age, gender), hospital stay, characteristics of the primary tumor, type of surgical resection and quality of resection. The length of the postoperative hospital stay period was defined as the interval from the day of surgery to discharge. The calculation for overall survival started at the date of surgery.

Pathological parameters analyzed were tumor diameter (T), regional lymph node status (N), resection margin status (R) and tumor grade (G). Furthermore, reports on distant metastasis (M) were also included. Grading was determined according to the ENETS guidelines [4]. Ki-67 immunohistochemistry was available in 31 tumor sections. When Ki-67 immunohistochemistry was not available, the histological report contained the mitotic count and/or clearly stated the tumor grading.

Postoperative pancreatic fistulas were defined according to the International Study Group of Pancreatic Surgery (ISGPS) [136].

For statistical analyses patients were divided into living and deceased patients. One patient (1,52 %) was lost for follow up and was excluded from statistical analyses regarding outcome. Patients who died within 30 days after operation were also excluded from these analyses.

Since the analysis period is long not all medical reports are complete. If this was the case and a detail was missing this patient was not considered for the special analysis.

With the clinical and histological information patients were subdivided into the two main classification systems – the ENETS and the UICC classification system.

3.2 Surgical procedures

Surgical strategy was based on anatomic and oncologic demands. According to the above mentioned findings the resection was planned and executed. For potentially malignant tumors in the head the classic pancreatic head resection or pylorus-preserving pancreaticoduodenectomy was chosen. For small and potentially benign tumors an organ-preserving approach was preferred. For left-sided lesions a distal pancreatectomy was chosen and if possible this was done spleen-preserving. Distal pancreatectomy was also done laparoscopically. Segmental pancreatic body resection was performed for central tumors and if necessary a total pancreatectomy was done in selected patients. Lymph nodes were dissected when extensive surgery was carried out. Debulking procedures where the primary tumor was resected were performed in combination with liver resection, hemicolectomy, splenectomy or gastric resection.

3.3 Statistical analysis

Overall survival, complication rates and other parameters (operation time, hospital stay) were assessed. An excel file was designed and these data were transferred into IBM SPSS Statistics 20. First a descriptive analysis was done.

For statistical analysis SPSS 20 was used. The survival rates were assessed with Kaplan-Meier methods and compared with the log rank test. Hazard ratios and corresponding confidence intervals (CI) were calculated. Only risk factors with a p-value of < 0,2 in univariate analysis were considered for multivariate analysis. The influence of variables was evaluated with the Cox regression model [137].

The morbidity was analyzed with Chi-square test in an univariate setting with crosstabs first. Thereafter, multiple logistic regression was used in the multivariate analysis. Again only variable with a p-value < 0,2 were considered for further analysis. Furthermore, regression coefficient and Hazard ratio with 95% confidence interval were collected [138].

A p-value < 0,05 was considered significant. If possible data were presented as mean values ± standard deviation.

The databank was established with Excel for mac 2011. Word for mac 2011 was used to write the thesis and references were managed with EndNote 6.0.2. Data are displayed either with SPSS 20 or with GraphPad prism version 4.0.

4 Results

4.1 Characterization of the analyzed group

The analysis included 66 patients, 33 female and 33 male. The analyzed cohort was of median age of 59,1 years (31 – 83). Figure 5 shows the distribution to different age groups with most patients operated between 60 – 69 years (31.8 %). The median age of patients was 62,5 years (31 – 83 years) at the time of the operation.

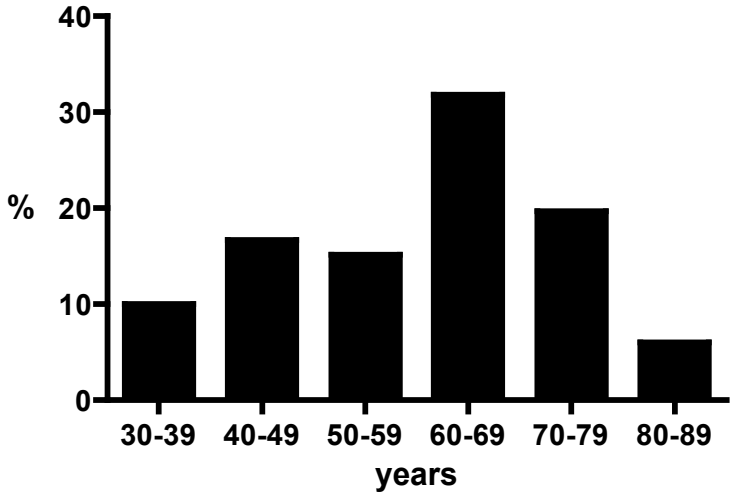

Fig. 5 Age pattern at the time of operation

The tumor of every patient investigated in this study was resected, hence the population does not include patients who only had undergone explorative laparotomy. Patients with pNET who are considered only for palliative care are also not included.

Various resection regimens were adopted to the patients. The tumor mass of 22 patients was resected via a pancreas head resection. Distal pancreatectomy was performed in 30 cases while complete pancreatectomy has do be done in five patients. Less invasive approaches were applied to eleven patients (five enucleations and four segmental resections). Resection of the tumor mass was accompanied in 35 % (n = 23) with an additional procedure like cholecystectomy or splenectomy.

Unfortunately the medical history of one patient is not complete, especially the histopathology report is inconclusive.

Furthermore, the postoperative outcome of one patient is not clear, as the patient could not be reached and the archive has only parts of the file. Therefore, the mentioned patient is not

included in calculations regarding the outcome.

The 30-day mortality in the analyzed group was 4,5 % (n=3), subsequently, these three patients were also excluded from any calculations concerning overall survival. Two of these three patients had a pancreatic head resection and one a distal pancreatectomy. Interestingly, all three patients had a history of pancreatitis, either prior to the operation or thereafter. The cause of death of one patient (head resection) was not directly related to the operation as this patient died because of heart failure. The two other patients suffered complications directly related to previous surgery and as a consequence re-operations were necessary. Nonetheless, both died of multi organ failure within 30 days.

female	n = 33
male	n = 33
age (years)	59,1 (31 - 83)
pancreatic head resection	n = 22
pancreatectomy	n = 5
distal pancreatectomy	n = 30
segmental resection	n = 9

Fig. 6 Characterization of the analyzed cohort

4.2 Surgery

As mentioned above different resection strategies were used for the diverse patients and tumor localizations. Five patients were treated with enucleation and four with segmental resection and as a consequence lymph node sampling was done only in 54 patients (84 %).

Five of the 30 (17 %) distal pancreatectomies were done via a laparoscopic approach. Lymph nodes were resected in four of these five cases (80 %). The laparoscopic approach required a mean operation time of 185 minutes (± 18,84 minutes) compared to 214,4 minutes (± 12,31 minutes) with the open procedure. This difference is statistically not significant.

Regarding the duration of the operation there is a statistically significant difference between deceased and living patients. Mean operation time of living patients was 183,1 minutes (± 12,74 minutes) and operation time of deceased patients averaged 253,7 minutes (± 19,19 minutes) (Figure 7 a). However, there was no significant difference in relation to the hospital stay between living and deceased patients (17,84 ± 2,18 days vs. 17,46 ± 1,41 days) (Figure

7 b). Furthermore, there is no significant difference evaluating the age of these two groups. Living patients were 58,18 years (± 2,29 years) at the time of operation, whereas the deceased population had a mean age of 60,37 years (± 2,57 years) (Figure 7 c).

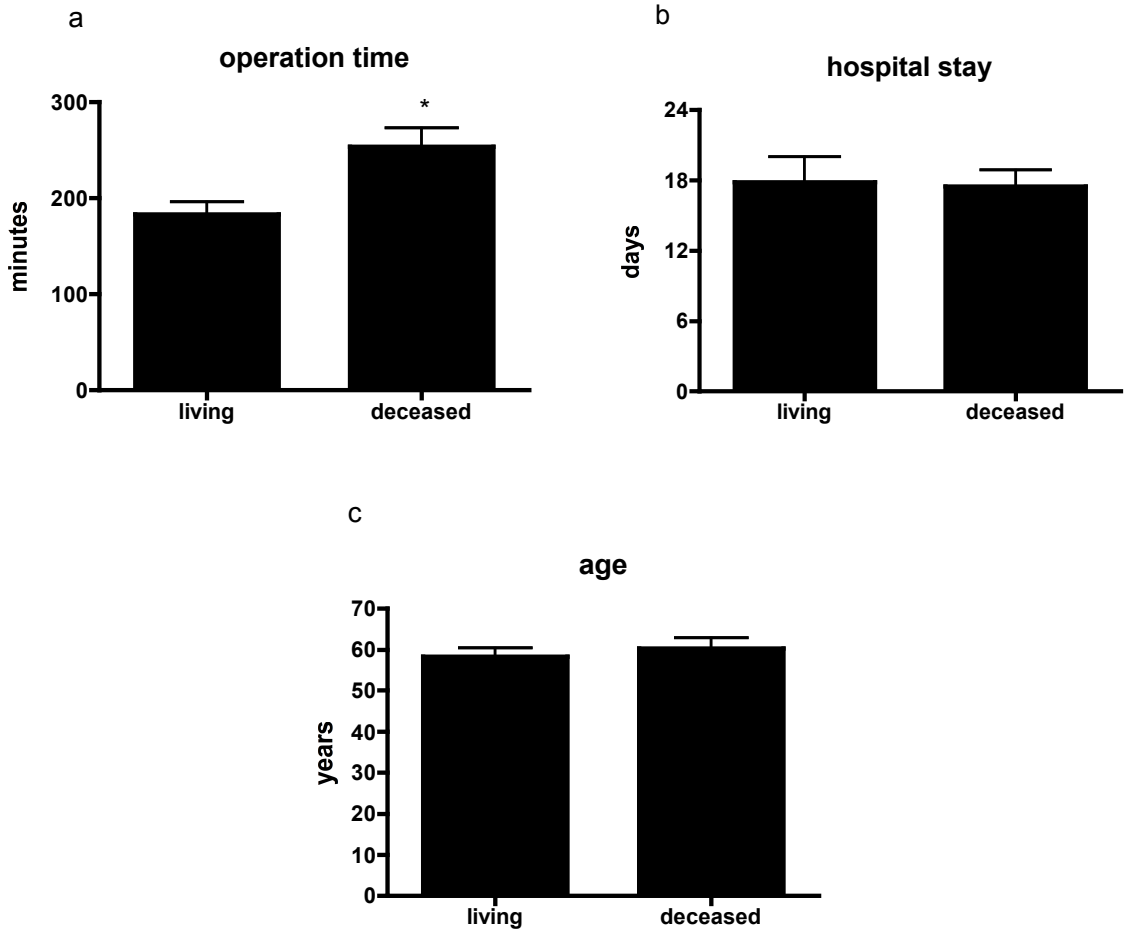

Fig. 7 a, b, c Differences between the operation time (a) (* $p < 0,05$), the hospital stay (b) and the age (c) of living and deceased patients.

In a subgroup analysis the different kinds of operations were analyzed. The operation time of the two main groups – pancreatic head resection and distal pancreatectomy – was evaluated. Neither was there a statistical significant difference of the operation time of the living and the deceased people in the pancreatic head resection group, nor was there a significant difference in the distal pancreatectomy group (Figure 8 a). The age at operation and the duration of the hospital stay were also compared in the above-mentioned collectives. Again there was no significant difference when the living and the deceased patients were compared to each other (Figure 8 b, c).

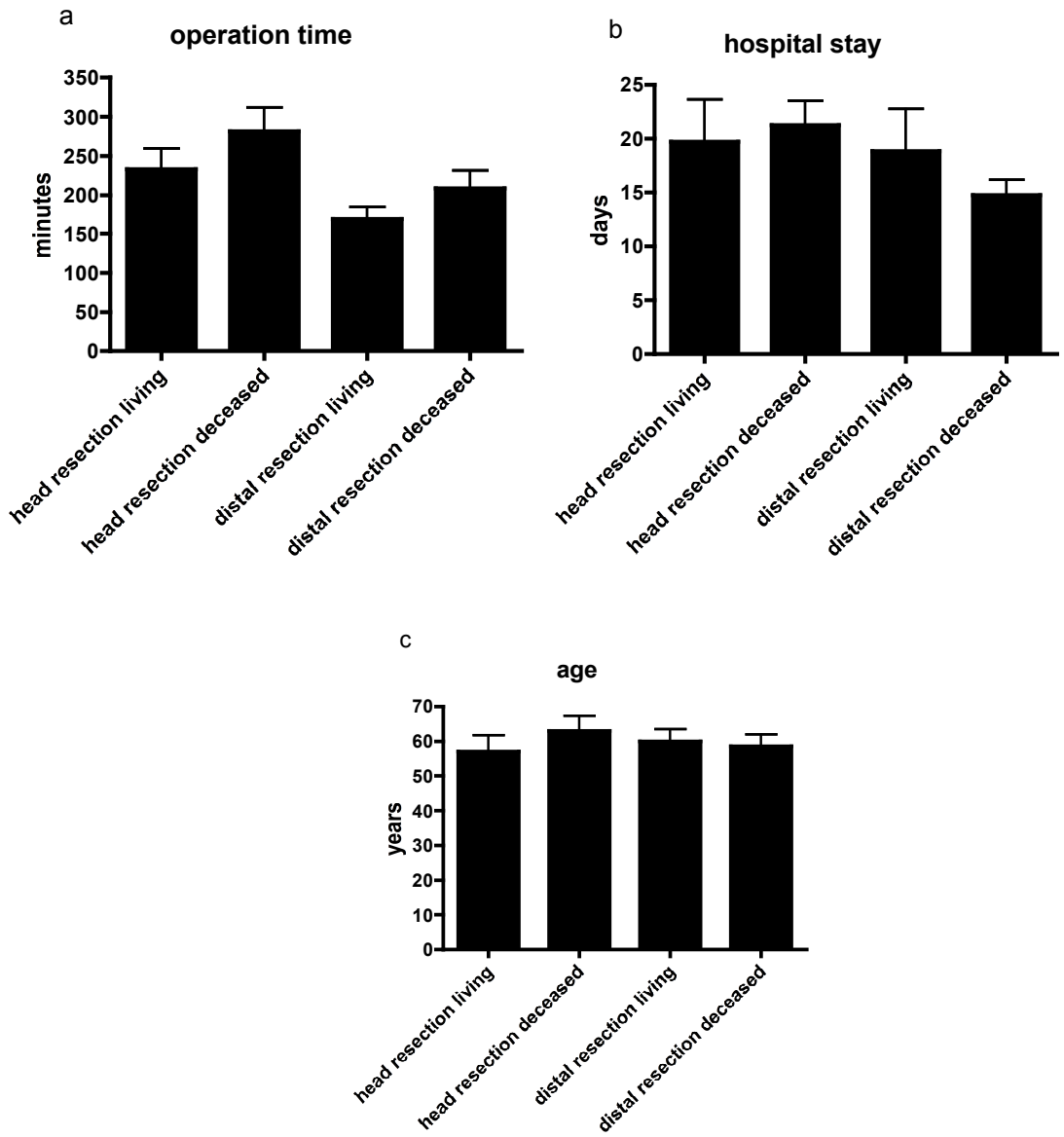

Fig. 8 a, b, c Differences between the operation time (a), the hospital stay (b) and the age (c) of living and deceased patients for the different operation regimes.

The cohort investigated in this study suffered from different complications. Pancreatic fistula was seen in 13 patients (19,7 %) and five patients required an interventional drainage (ISGPS B).

25 patients of the analyzed cohort received any kind of anastomosis and anastomotic leakage developed in nine of these patients (36 %). Only one patient developed a leakage of the gastrojejunostomy and subsequent operation was necessary in this patient because of the insufficiency. An insufficiency of the pancreaticojejunostomy was detected in 3 patients. The most common kind of anastomotic leakage was an insufficiency of the hepaticojejunostomy, which was observed in five patients. Moreover, four of these patients

necessitated reoperation due to the insufficiency.

Six patients (9,1 %) of the investigated cohort had to be re-operated because of a complication. Four patients suffered from an insufficiency of the hepaticojejunostomy, one patient had an insufficiency of the gastrojejunostomy and one patient developed a pancreatitis after the initial tumor operation.

4.3 Overall survival

As mentioned above the postoperative outcome of one patient (1,5 %) is unknown and three patients are excluded from any survival calculation as they died within 30 days. As a consequence the calculation of the overall survival rate contains 62 patients. The median follow up period was 51 months (6 – 220 months) and the calculated mean overall survival was 130,17 months (CI95%: 103,21 – 157,14 months). The survival rate after one year was 95 %, after two years still 87 % and after three years 80 %. The calculated 5-year survival for the analyzed cohort was 66 %. Figure 9

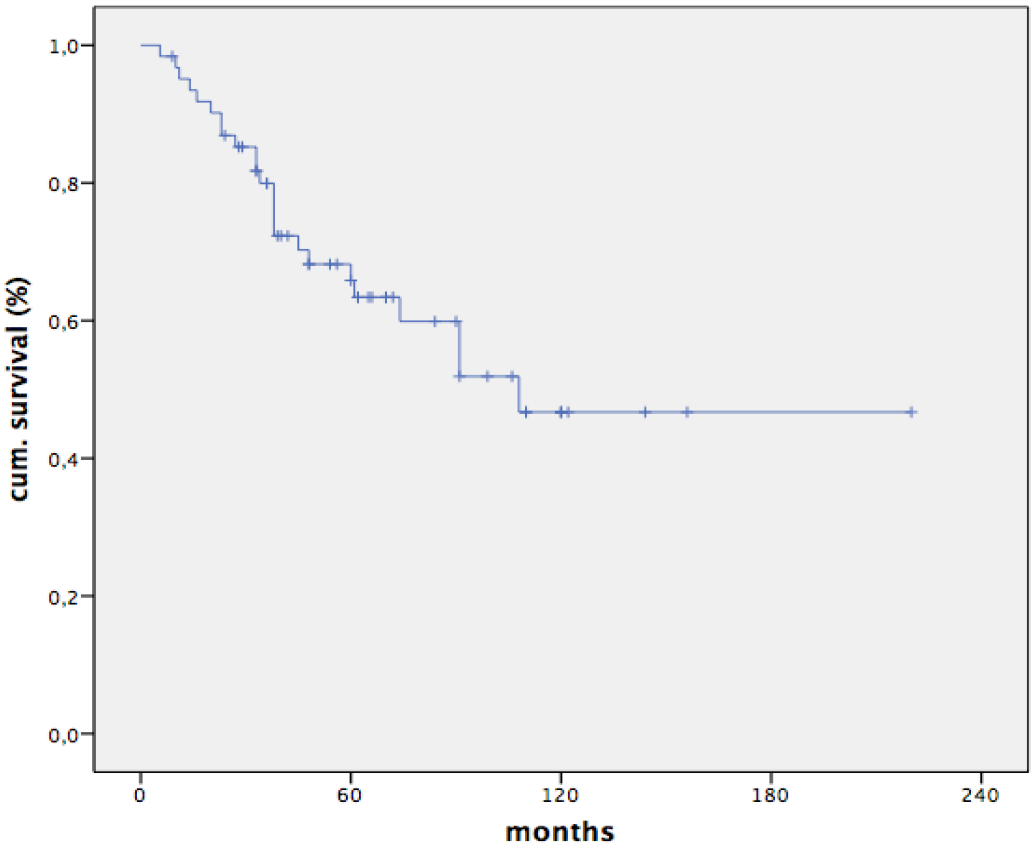

Fig. 9 Calculated overall survival

4.3.1 Overall survival in regard to gender

The survival rates of female and male patients were compared next. The distribution to the two groups was exactly equal, 31 female and 31 male patients. The survival rates did not differ significantly between the two groups. The calculated mean overall survival for female patients was 151,37 months (CI95%: 117,03 – 185,72) compared to 79,3 months (CI95%: 63,53 – 95,08) for male patients (p=n.s.). Figure 10

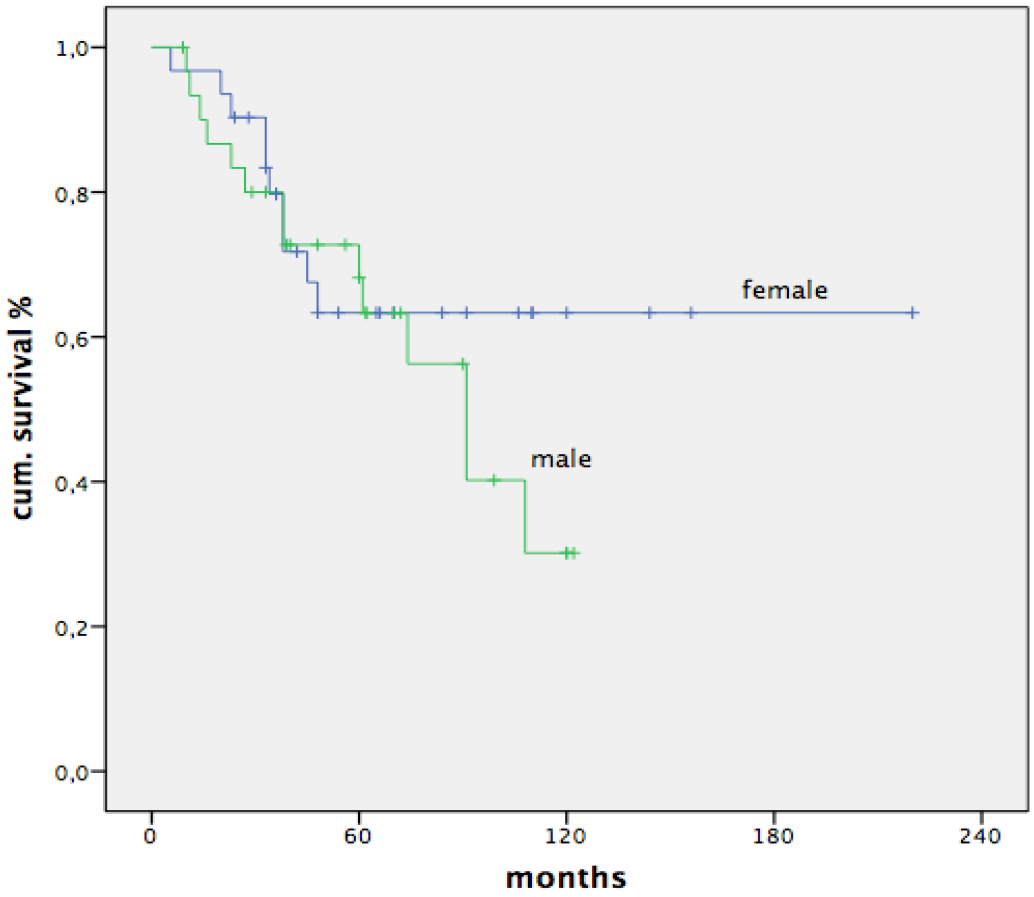

Fig. 10 Survival rate regarding the gender of the patients (p=n.s.). Blue line: female, green line: male

4.3.2 Overall survival in regard to age

The impact of the age of patients at the time of operation was also highlighted. Our analysis revealed no influence of the age since overall survival rates were not significantly different if patients were younger or older than the median. The calculated mean overall survival for patients who came below the median was 146,06 months (CI95%: 110,1 – 182,02). Patients exceeding the median age reached a calculated mean overall survival of 75,13 months (CI95%: 58,21 – 92,05) (p=n.s.). Figure 11

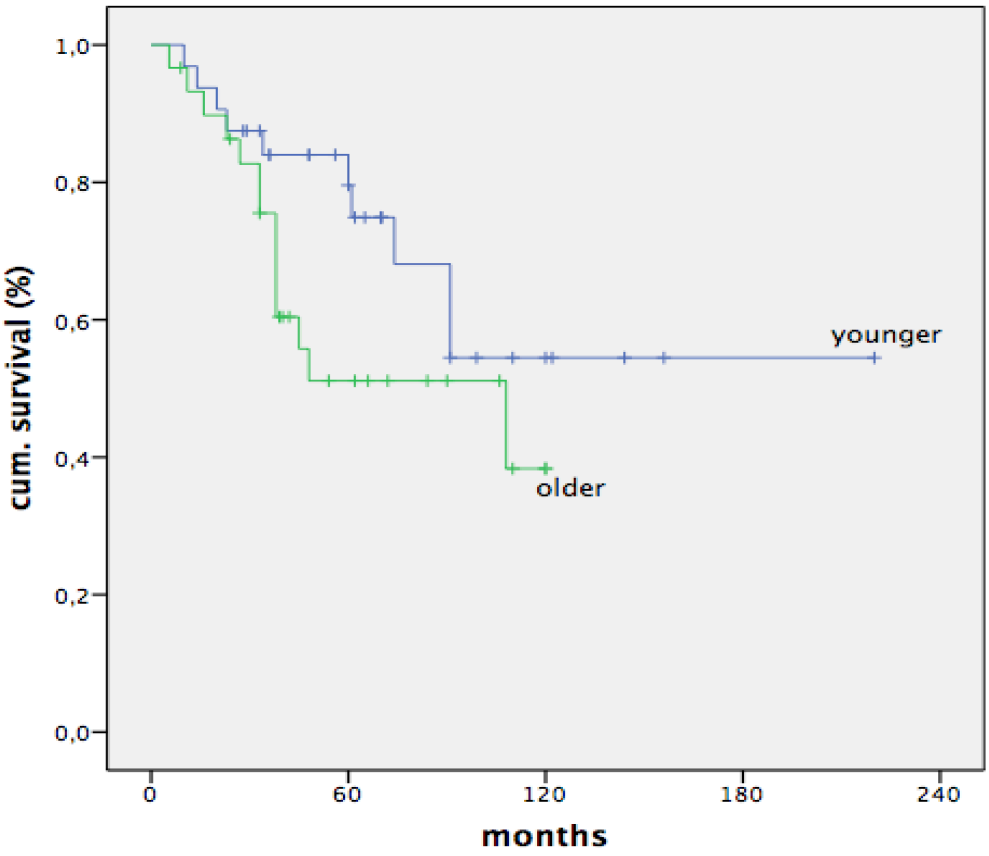

Fig. 11 Survival rate regarding the age of the patients (p=n.s.). Blue line: younger than median, green line: older than the median age

4.4 TNM assessment and survival

Clinical report on tumor size, lymph nodes, metastasis and resection status is missing for only one patient (1,5 %), however, a report on the tumor grading is available for this patient. Four patients were excluded from the calculation of the survival rates as three died within 30 days in hospital and one patient is lost for follow up.

4.4.1 Tumor size (T)

As mentioned above the tumor size of one patient is missing. 19 patients of the 65 patients were categorized to have a T1 tumor (29,2 %) and the patient lost for follow up had a T1 tumor. T2 tumors were found in 14 patients (21,5 %), T3 tumors represent the biggest group with 25 patients (38,5 %) and T4 pNETs were found in 7 patients (10,8 %).

Within these four groups the 3-year survival was best for patients with small tumors. This population showed a 3-year survival of 78 %, compared to a 3-year survival rate of 66 % in the T4 group. The 3-year survival rates for the T2 group and the T3 group are comparable to T1-tumors with 77 % and 75 %, respectively. The calculated mean overall survival of patients with a T1 tumor was 80,43 months (CI95%: 62,67 – 98,19 months) and patients with a T2 tumor had an even better mean overall survival of 90,93 months (CI95%: 67,53 – 114,32 months). The best calculated mean overall survival showed patients with a T3 tumor 118,89 months (CI95%: 79,89 – 157,9 months). Lastly, T4 tumors had the worst outcome with a mean overall survival of 72 months (CI95%: 38,5 – 105,5 months). Figure 12.

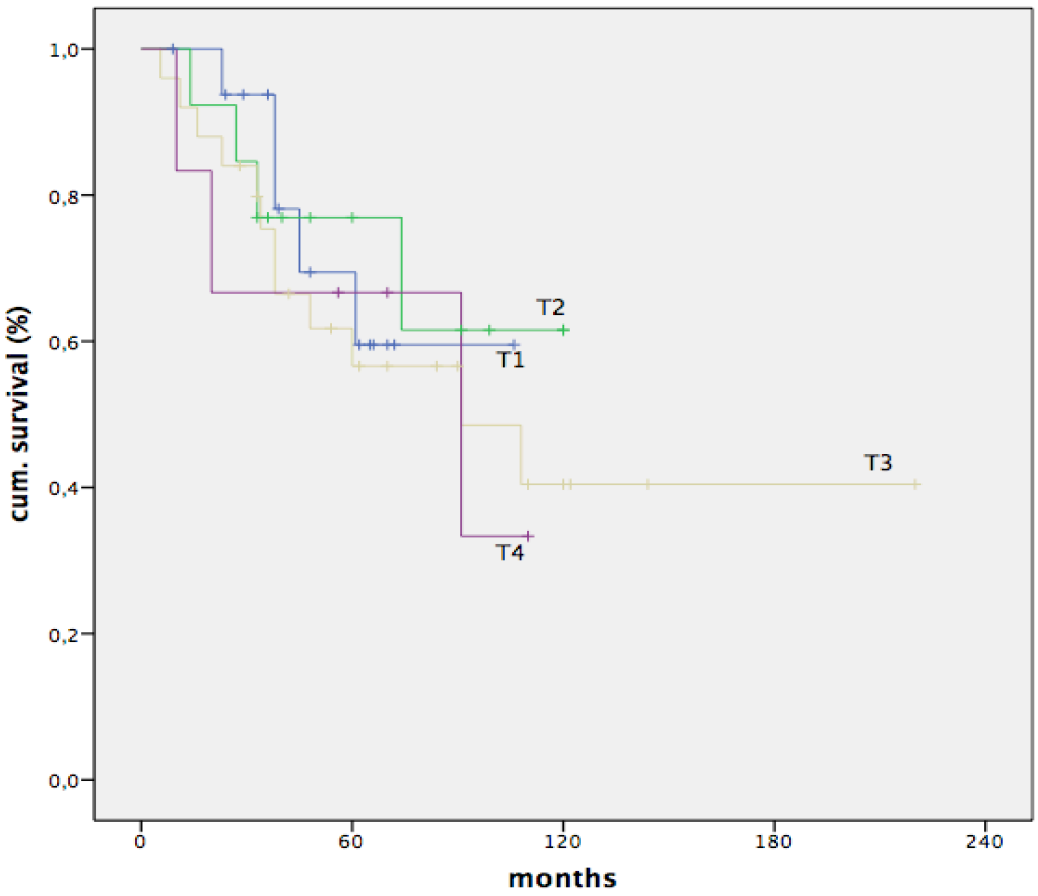

Fig. 12 Calculated survival rates illustrating the tumor size (T).

4.4.2 Lymph node (N) status

Due to divergent operation methods and the partly missing medical history of one patient TNM assessment is not possible in every case. Besides the tumor mass lymph nodes were resected in 81,8 % (n=54), hence TNM staging is possible in these cases. The majority of these 54 patients did not show any positive lymph node (n=36; 66,7 %), however 18 patients (33,3 %) had at least one positive lymph node. No lymph node sampling was done in 11 patients and the medical history of one patient is inconclusive regarding the lymph node status (18,2 %).

The 3-year survival rates do not differ largely. Patients with no lymph node metastasis (N0) showed a 3-year survival rate of 77 % and patients with at least one positive lymph node (N1) reached 75 % survival after three years. This difference was statistically not significant (p=n.s.). Not surprisingly was the 3-year survival rate of patients with no lymph nodes resected best with 100 %.

The calculated mean overall survival was concordant to the 3-year survival rates. Patients with no lymph node metastasis had a mean overall survival of 75, 58 months (CI95%: 59,96 – 91,19 months) and patients with positive lymph nodes even 121,92 months (CI95%: 71,96 –171,88 months). The best calculated mean overall survival had patients with no lymph node resected 139,75 months (CI95%: 112,17 – 167,33 months). Figure 13.

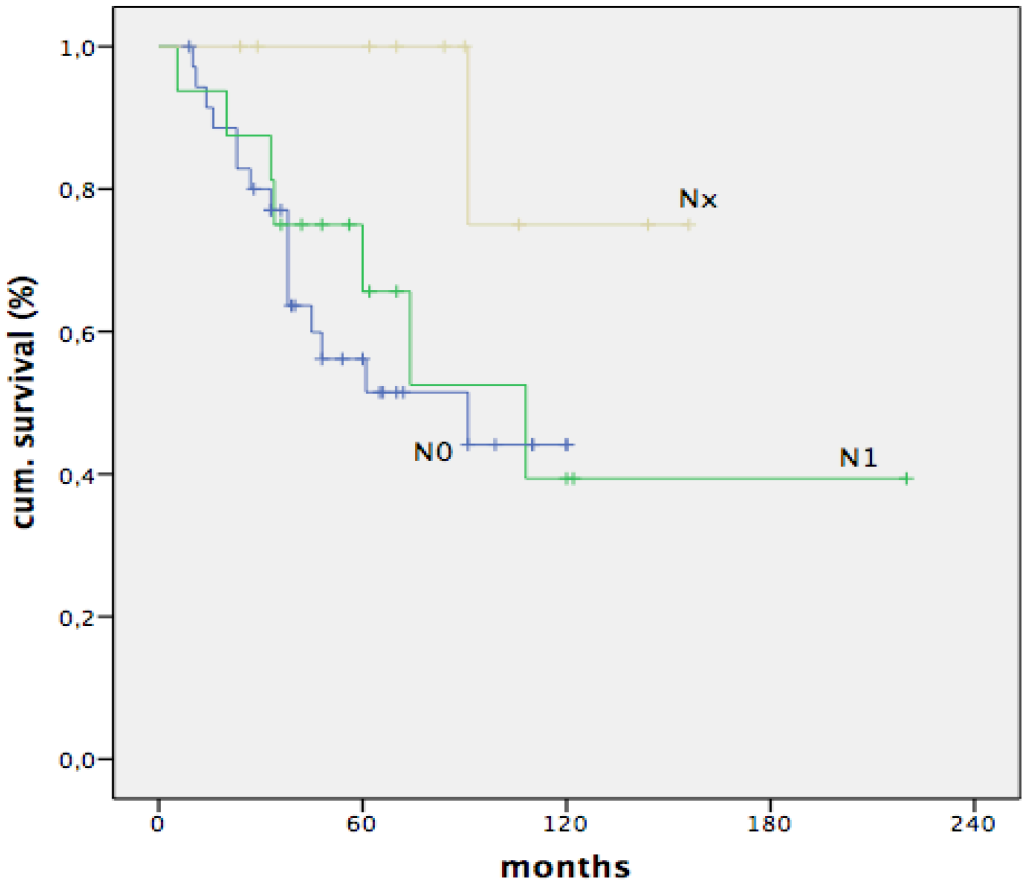

Fig. 13 Calculated survival rates illustrating the lymph node status (N) (N0 vs. N1, p=n.s).

4.4.3 Metastasis (M) status

The medical reports about distant metastasis are complete for all 66 patients. When the operation was carried out 52 patients did not have distant metastases (M0; 78,8 %), however, 14 patients (21,2 %) had already a metastatic disease (M1).

In an univariate analysis the two groups, either M0 or M1, showed statistical significant difference in survival rates. The 3-year survival rate for M0-patients was 85 % and for M1-patients 60 % (p<0,05). These findings were confirmed by the calculated mean overall survival which was 150,23 months (CI95%: 120,08 – 180,39 months) for M0-patients and patients with a metastatic disease reached 48,83 months (CI95%: 29,9 – 67,76 months). Figure 14.

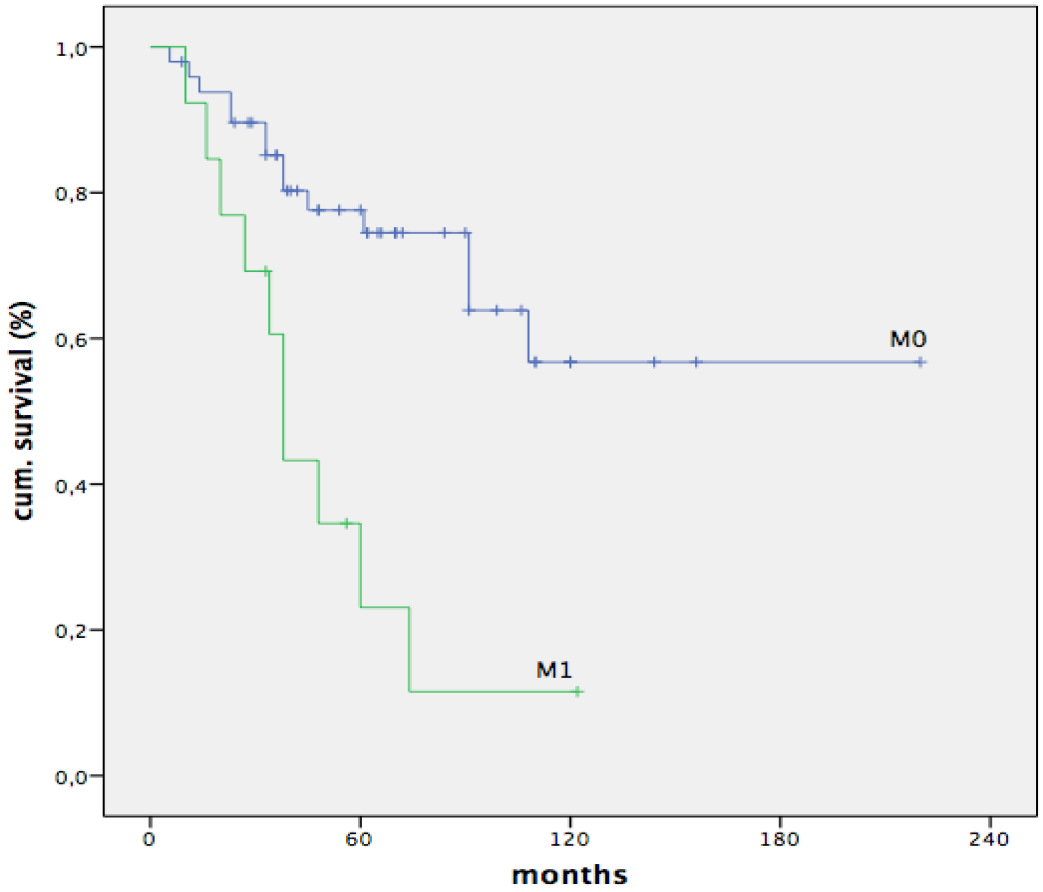

Fig. 14 Calculated survival rates illustrating the metastatic status (M) (p<0,05).

4.4.4 Resection (R) status

The results concerning the resection status are complete for all patients. The tumor mass of the big majority of patients (n=55; 83,3 %) was resected in sano (R0). However, the resection margins were not tumor free (R1) in eleven patients (16,7 %).

The univariate analysis of the resection margins highlighted a statistical significant difference of the 3-year survival rates for R0 and R1. The population with a tumor free resection margin had a 3-year survival rate of 86 %, compared to 55 % in the R1 group ($p<0,05$). Patients with a tumor free resection margin showed a calculated mean overall survival of 152,07 months (CI95%: 123,74 – 180,4 months), however, patients with tumor infiltrated resection margins had only a mean overall survival of 51,65 months (CI95%: 28,09 – 75,2 months). Figure 15.

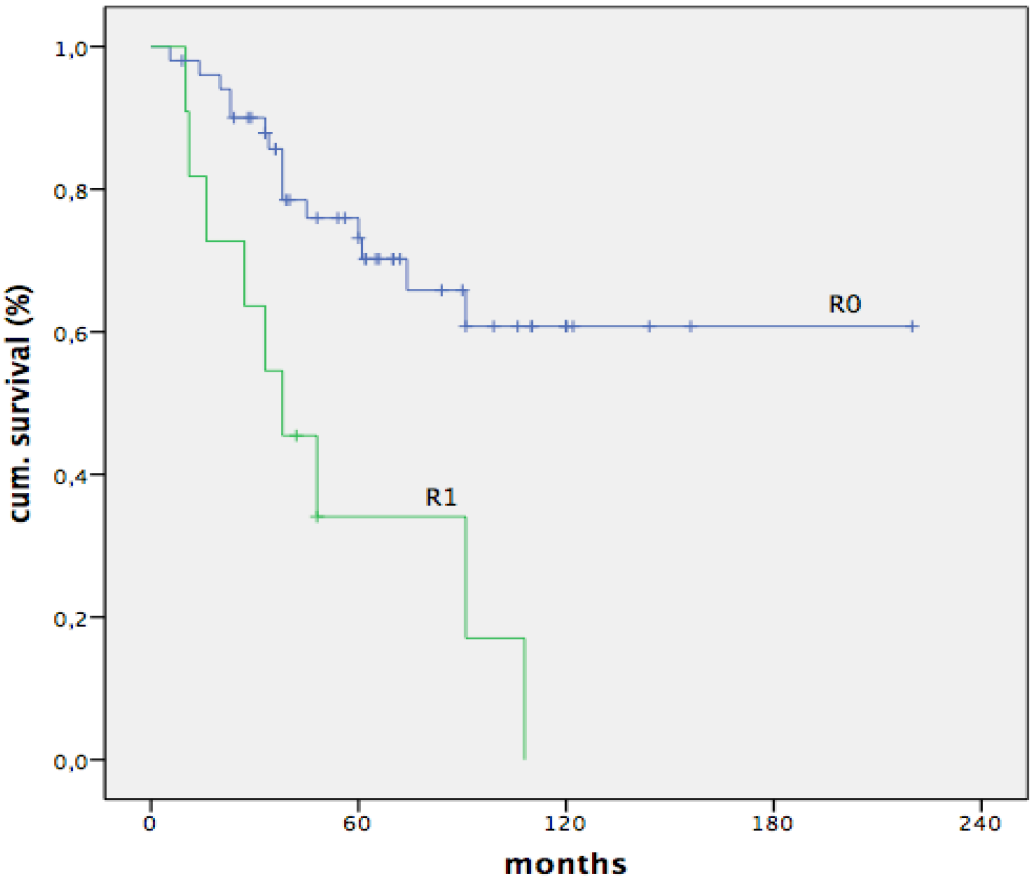

Fig. 15 Calculated survival rates illustrating the resection margin (R) ($p<0,05$).

4.4.5 Grading (G) status

The grading is conclusive for each patient. The biggest group represented G1 tumors with 45 patients (68,2 %). The other third of the analyzed cohort were distributed to G2 and G3 as follows. 15 patients (22,7 %) were classified with a G2 tumor and 6 patients (9,1 %) were resected suffering from a G3 carcinoma. Taken together, G1 and G2 tumors represent the majority of resected tumors (91,4 %).

The 3-year survival rate of the patients with a G1 tumor was 87 % and the G2 group showed a 3-year survival rate of 80 %. The group with G3 tumors was inferior to the other two with a 3-year survival rate of only 33 %. As expected the calculated mean overall survival was best for patients with a G1 tumor 164,14 months (CI95%: 133,9 – 194,39 months). The G2-group reached a mean overall survival of 87,93 months (CI95%: 58,18 – 117,68 months) and the G3-group showed the worst mean overall survival of 37,17 months (CI95%: 7,86 – 66,47 months). Figure 16.

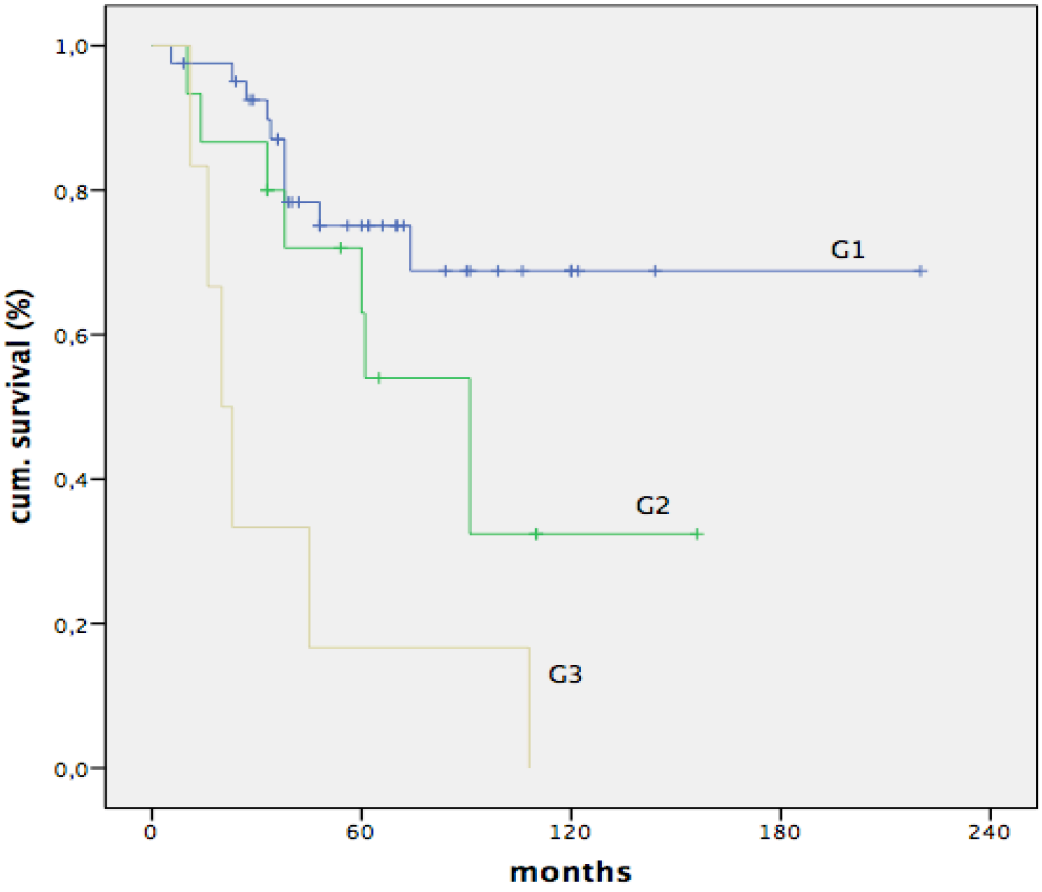

Fig. 16 Calculated survival rates illustrating the grading (G).

4.5 Lymph node and distant metastases

In this chapter we analyzed the probability to develop lymph node or distant metastases. We found a correlation between tumor size and the rate of lymph node metastases. For these calculations only operations were considered within which lymph nodes were sampled. Therefore we analyzed the files of 54 patients.

4.5.1 Correlation of tumor size and lymph node metastases

We found a correlation between tumor size and the probability of positive lymph nodes. One patient (8,33 %) with a T1 tumor had positive lymph nodes and four (28,57 %) with a T2 tumor. This rate increases if there was a T3 or T4 tumor found. Nine patients (36 %) with a T3 tumor and four patients (66,67 %) with a T4 had lymph node metastases. The increase is obvious from group to group, however only the difference between T1 and T4 is statistically significant. Figure 17

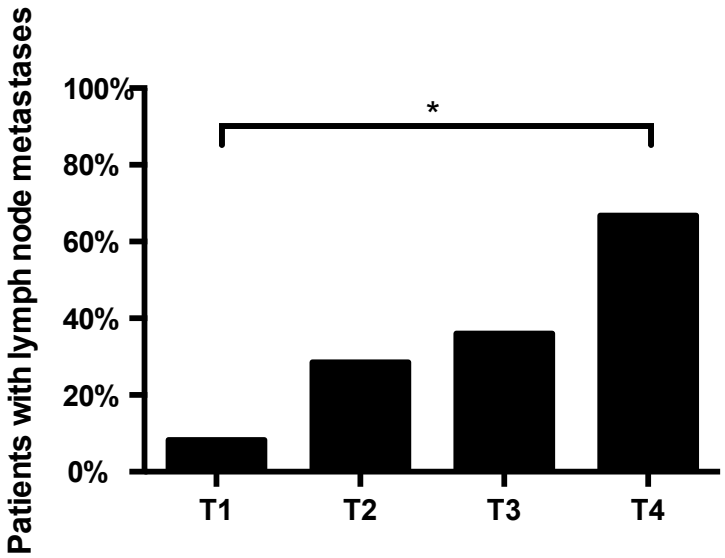

Fig. 17 Correlation of tumor size and the probability of lymph node metastases. (* p<0,05)

4.5.2 Correlation of tumor size and distant metastases

There was also an increase in the probability to have distant metastases at the time of operation when the primary tumor was bigger. Again only one patient (5,26 %) with a T1 tumor and only two patients (14,29 %) with a T2 tumor had distant metastases. Seven patients (28 %) with a T3 tumor suffered from distant metastases and four (57,14 %) with a T4 tumor. The difference from T1 and T2 to T4 was statistically significant. Figure 18

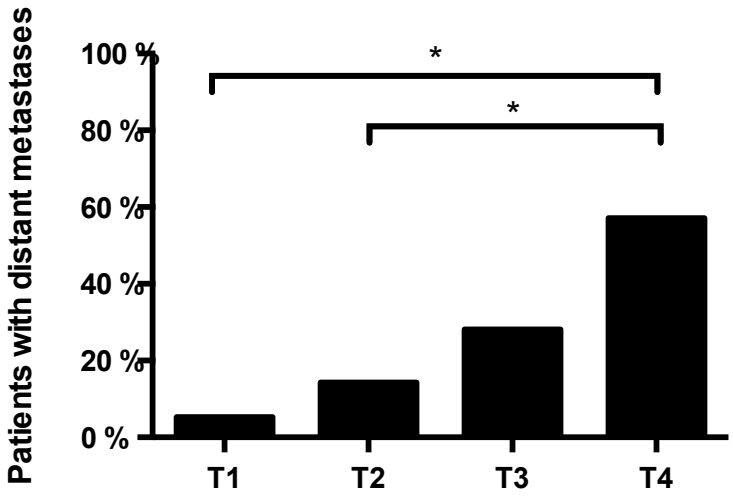

Fig. 17 Correlation of tumor size and the probability of distant metastases. (* p<0,05)

4.6 ENETS and UICC classification

After TNM assessment the patients were further subdivided according to the two main classification systems, the ENETS and the UICC classification system. For exact classification the histopathology has to contain full information on TNM. As mentioned above almost the entire medical history of one patient is missing and twelve operations were carried out without resecting any lymph nodes and as a consequence classification to either group is not feasible in these special cases.

Therefore we find 54 patients in the ENETS classification system subdivided into one of the following groups. In group I are ten patients (18,5%) and in II A are nine patients (16,7 %), again in group II B are ten patients (18,5 %). Group III A contains no patient, however, III B has eleven patients (20, 4 %) and group IV represents even the largest cohort with 14 patients (25,9 %). Figure 18 a

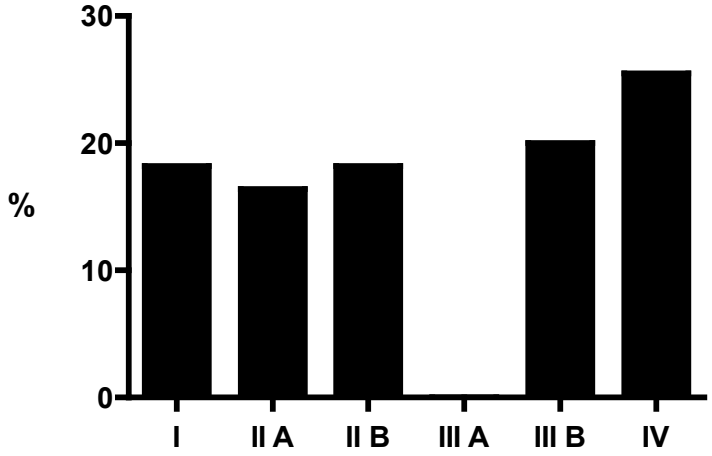

Fig. 18 a Distribution according to the ENETS classification system

The UICC group I A contains ten patients (18,5 %) and group I B nine patients (16,7%). The groups II A and II B have nine (16,7%) and ten (18,5 %) patients, respectively. Group III consists of two patients (3,7 5%) and group IV of 14 patients (25,9 %). Figure 18 b

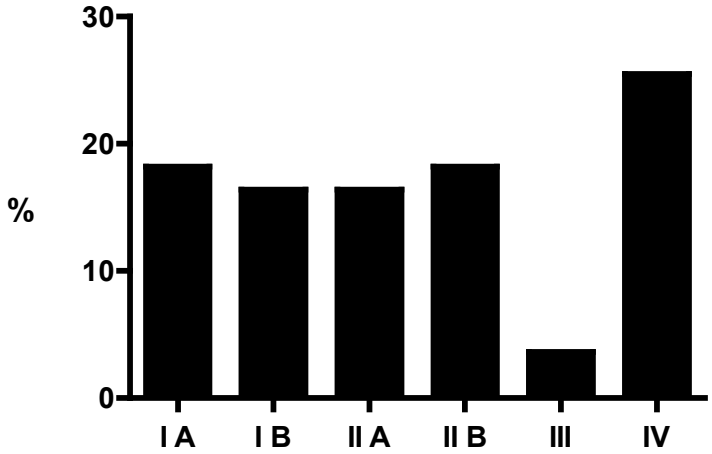

Fig. 18 b Distribution according to the UICC classification system

4.7 Survival rates for ENETS and UICC classification system

The survival rates were calculated for both main classification systems – ENETS and UICC. One patient in the entire cohort was lost for follow up, but no lymph nodes were resected in this patient. Hence, this patient was not classified into ENETS or UICC classification system.

The three patients who died within 30 days are also excluded from this calculation. No lymph nodes were resected of one of these three patients and therefore could not be classified to one of the groups.

4.7.1 Survival rates for ENETS classification system

Patients were distributed in almost every group, with exception of group III A. The 3-year survival rates of the different groups were as follows. Group I had a 3-year survival rate of 89 %. Groups II A and IIB reached 78 % and 80 %, respectively. No patient matched in group III A, but group III B showed a 3-year survival rate of 80 % as well. The worst result showed group IV with a 3-year survival rate of 60 %. The calculated mean overall survival rates of the different groups were as follows: Group I had a calculated mean overall survival of 57,5 months (CI95%: 45,88 – 69,11 months), group II A 98,56 months (CI95%: 72,18 – 124,93 months), group II B 85,06 months (CI95%: 57,51 – 112,61 months), group III B 149,98 months (CI95%: 87,21 – 212,76 months) and group IV 48,83 months (CI95%: 29,9 – 67,76 months). Figure 19.

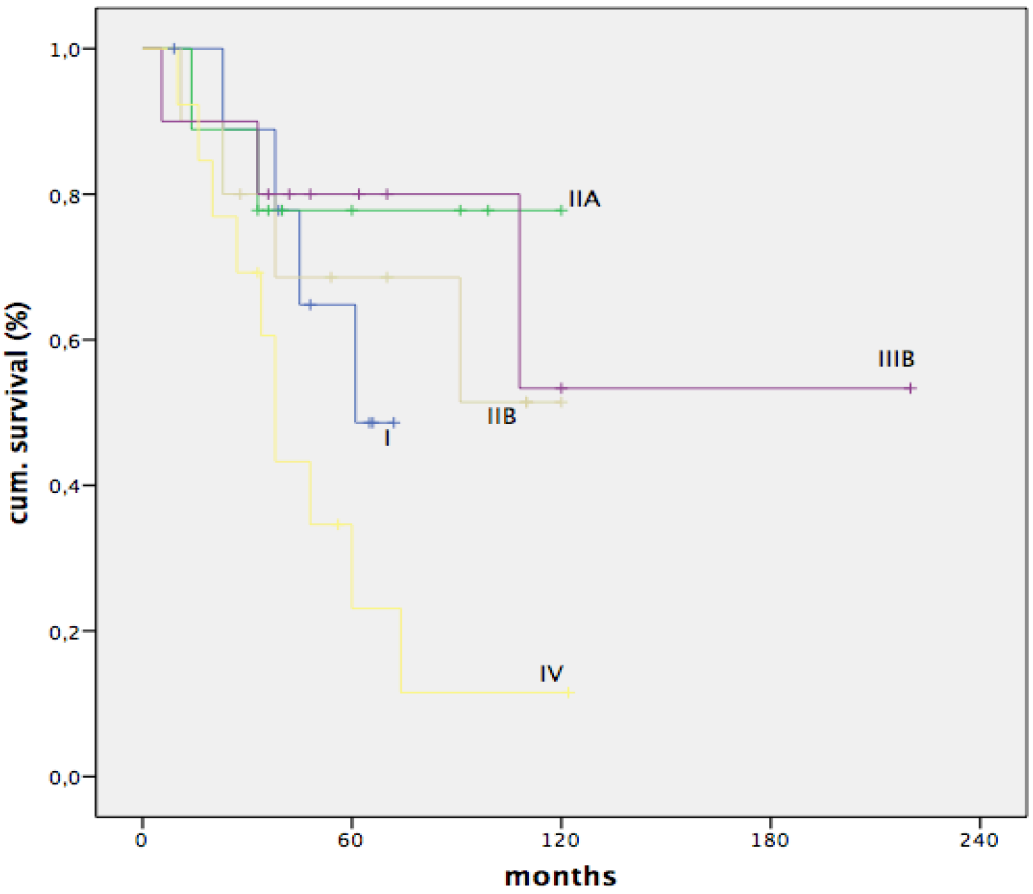

Fig. 19 ENETS classification survival.

4.7.2 Survival rates for UICC classification system

In contrast to the ENETS classification system every group within the UICC classification system was occupied. Group I A had the same survival rate than ENETS group I (89 %). Furthermore, correlated group I B with ENETS group II A. The survival rate for both groups was 78 %. The 3-year survival rates of group II A and II B reached both 78 %. Astonishingly, group III had the best survival rate with 100 %, however only two patients fulfilled the criteria for this group. Since the requirements for stage IV were the same in both classification systems, the 14 patients had the same 3-year survival rate of 60 %. The diverse calculated overall survival times of the UICC classification were not as expected. The second worst survival time had group I A with 57.5 months (CI95%: 45,88 – 69,11 months), however, second best survival rate was reached within group I B with 98,56 months (CI95% 72,18 – 124,93 months). Since there was no death within group III survival rate was 100 %. The difference between II A and II B was also huge. Group II A achieved a calculated survival rate of 80,22 months (CI95%: 50,67 – 109,76 months) compared to 146,35 (CI95%: 81,91 – 210,75 months), which was even the best survival rate. Group IV had the worst survival rate with 48,83 months (CI95%: 29,9 – 67,76 months). Figure 20.

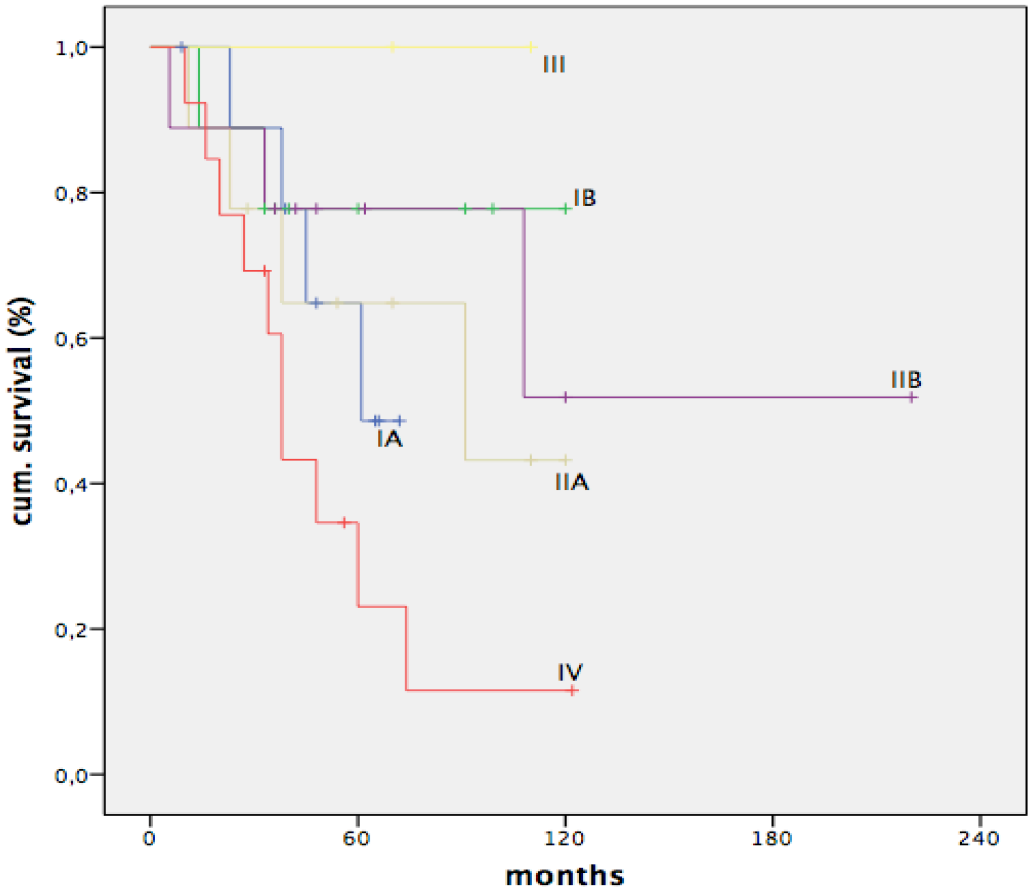

Fig. 20 UICC classification survival.

4.8 Survival rates in regard to surgery

4.8.1 Operation time

Firstly the median operation time was calculated, in which the two groups showed an equivalent distribution. The median operation time was 192,5 minutes. There was a statistically significant difference regarding the survival when the operation time exceeded the median operation time. Patients with a shorter operation time had a better survival. In our patients the calculated median overall survival was 163,63 months (CI95%: 129,73 – 197,52) if the median operation time was not exceeded. This rate decreases to 70,26 months (CI95%: 53,8 – 86,73) when the operation took longer than the median duration of 192,5 minutes (p<0,05). Figure 21.

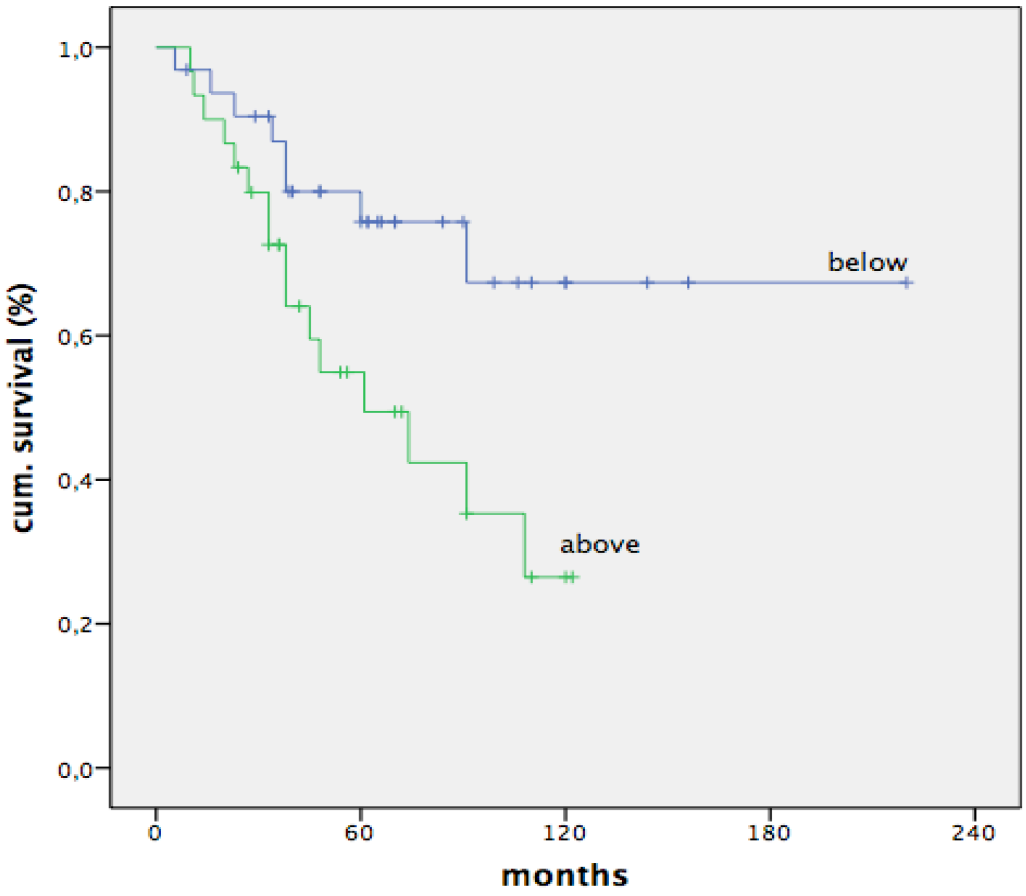

Fig. 21 Survival rate regarding operation time (p<0,05). Green line: exceeding the median operation time, blue line: below the median operation time.

4.8.2 Type of surgery

In a next step the two main groups of surgery (pancreatic head resection, distal pancreatectomy) were analyzed. The outcome did not differ no matter which type of operation was carried out. The calculated median overall survival if a distal pancreatectomy was done was 135 months (CI95%: 97,42 – 172,63) compared to otherwise operated patients with 83,72 months (CI95%: 67,91 – 99,54) (p=n.s.). Figure 22 a.

When a pancreatic head resection was performed there was also no significant difference in the calculated overall survival rates. Patients undergone a major resection survived 136,5 months (CI95%: 103,37 – 169,62) compared to 72,52 months treated with a different procedure (CI95%: 50,91 – 94,14) (p=n.s.). Figure 22 b.

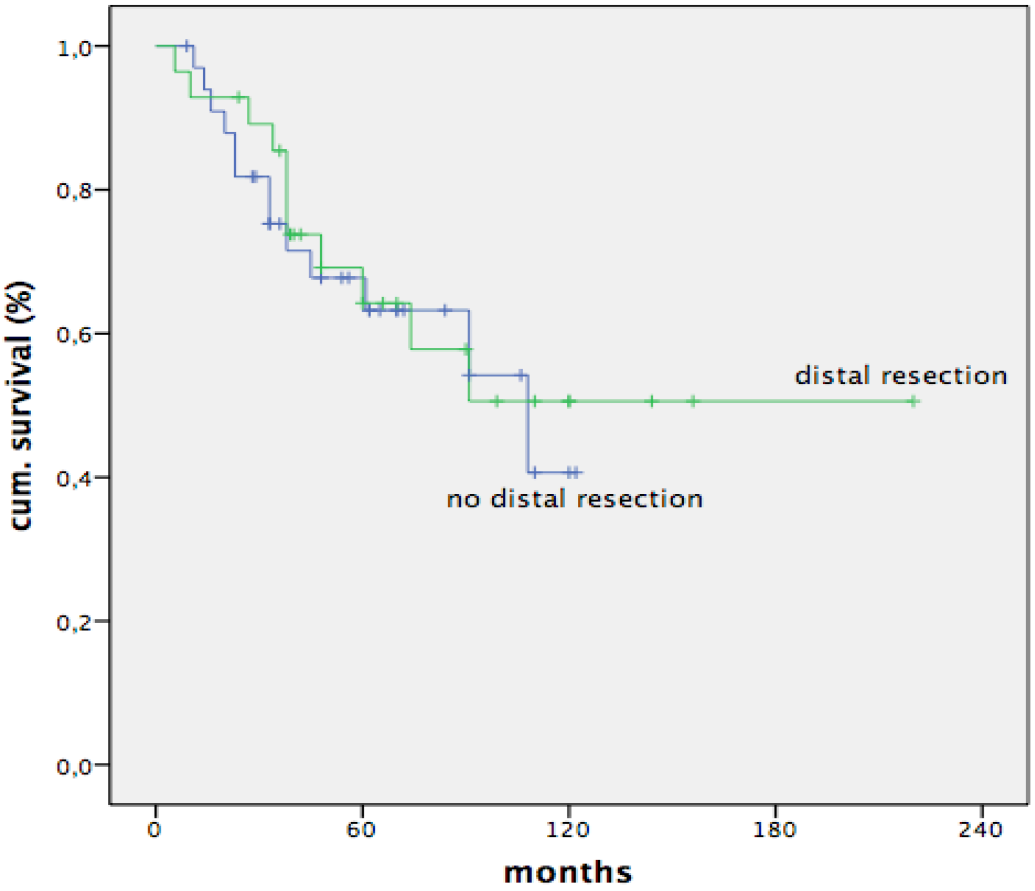

Fig. 22 a Survival rate of distal pancreatectomy (p=n.s.). Green line: distal pancreatectomy, blue line: other operation.

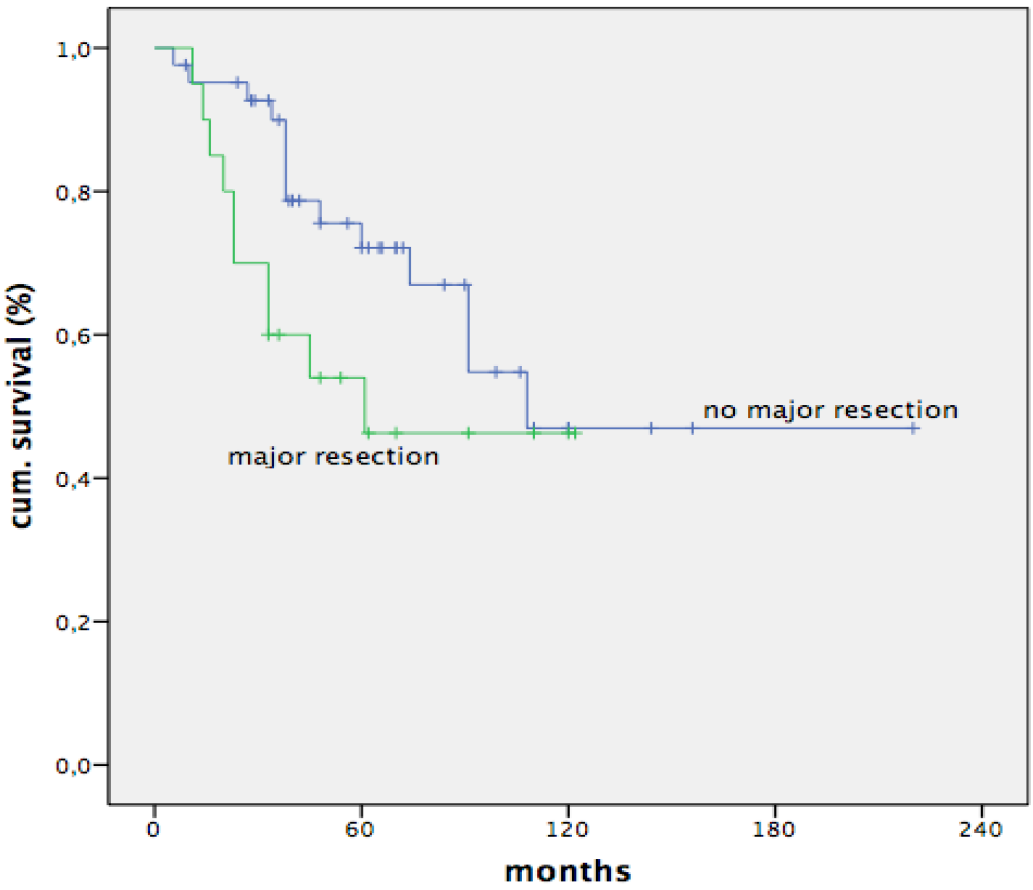

Fig. 22 b Survival rate of pancreatic head resection (p=n.s.). Green line: pancreatic head resection, blue line: other operation.

4.9 Univariate analysis of severe complications

The cohort was analyzed in an univariate approach concerning severe complications according to the classification system by Dindo et al. In this publication Dindo and coworkers classified complications from grade I to grade V. The grades range from not serious grade I complications to death of the patient (grade V) [139].

In this setting a severe complication was classified as grade III-a or higher. Grade III complications are defined as complications requiring surgical, endoscopic or radiologic intervention without (III-a) or with (III-b) general anesthesia. In this calculation the entire cohort was included since the direct postoperative morbidity is known for every patient.

4.9.1 Severe complications and operation time

Firstly, the operation time as a risk factor for severe complications was analyzed. In the univariate analysis the operation time was no significant risk factor. Nonetheless, there was trend as the one-sided chi-square test was statistically significant. Figure 23

OP Dauer ueber Median? * Schwere Komplikationen? Kreuztabelle

			Schwere Komplikationen?		
			nein	ja	Gesamt
OP Dauer ueber Median?	nein	Anzahl	26	7	33
		% innerhalb von OP Dauer ueber Median?	78,8%	21,2%	100,0%
	ja	Anzahl	18	15	33
		% innerhalb von OP Dauer ueber Median?	54,5%	45,5%	100,0%
Gesamt		Anzahl	44	22	66
		% innerhalb von OP Dauer ueber Median?	66,7%	33,3%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	4,364[a]	1	,037		
Kontinuitätskorrektur[b]	3,341	1	,068		
Likelihood-Quotient	4,440	1	,035		
Exakter Test nach Fisher				,066	,033
Zusammenhang linear-mit-linear	4,298	1	,038		
Anzahl der gültigen Fälle	66				

Fig. 23 Univariate analysis of the operation time and severe complications (p=n.s.)

4.9.2 Severe complications and age

The question was, if the age of the patient is a risk factor to develop a severe complication. In our cohort there was no significant correlation of age and severe complications. (p=n.s.) Figure 24

Alter ueber dem Median? * Schwere Komplikationen? Kreuztabelle

			Schwere Komplikationen?		
			nein	ja	Gesamt
Alter ueber dem Median?	nein	Anzahl	23	10	33
		% innerhalb von Alter ueber dem Median?	69,7%	30,3%	100,0%
	ja	Anzahl	21	12	33
		% innerhalb von Alter ueber dem Median?	63,6%	36,4%	100,0%
Gesamt		Anzahl	44	22	66
		% innerhalb von Alter ueber dem Median?	66,7%	33,3%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	,273[a]	1	,602		
Kontinuitätskorrektur[b]	,068	1	,794		
Likelihood-Quotient	,273	1	,601		
Exakter Test nach Fisher				,794	,397
Zusammenhang linear-mit-linear	,269	1	,604		
Anzahl der gültigen Fälle	66				

Fig. 24 Univariate analysis of the age and severe complications (p=n.s.)

4.9.3 Severe complications and gender

In the next analysis the influence of the gender of a patient on severe complications was examined. There was no significant difference between female and male patients. (p=n.s.) Figure 25

Geschlecht * Schwere Komplikationen? Kreuztabelle

			Schwere Komplikationen?		
			nein	ja	Gesamt
Geschlecht	weiblich	Anzahl	23	10	33
		% innerhalb von Geschlecht	69,7%	30,3%	100,0%
	maennlich	Anzahl	21	12	33
		% innerhalb von Geschlecht	63,6%	36,4%	100,0%
Gesamt		Anzahl	44	22	66
		% innerhalb von Geschlecht	66,7%	33,3%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	,273[a]	1	,602		
Kontinuitätskorrektur[b]	,068	1	,794		
Likelihood-Quotient	,273	1	,601		
Exakter Test nach Fisher				,794	,397
Zusammenhang linear-mit-linear	,269	1	,604		
Anzahl der gültigen Fälle	66				

Fig. 25 Univariate analysis of the gender and severe complications (p=n.s.)

4.9.4 Severe complications and pancreatic head resection

The type of surgery was also topic of the univariate analysis. There were not more severe complications when a pancreatic head resection was performed. The one-sided chi-square test was significant suggesting a tendency to more complications when a more extensive resection was carried out. (p=n.s.) Figure 26

Pankreaskopfresektion? * Schwere Komplikationen? Kreuztabelle

			Schwere Komplikationen?		
			nein	ja	Gesamt
Pankreaskopfresektion?	nein	Anzahl	33	11	44
		% innerhalb von Pankreaskopfresektion?	75,0%	25,0%	100,0%
	ja	Anzahl	11	11	22
		% innerhalb von Pankreaskopfresektion?	50,0%	50,0%	100,0%
Gesamt		Anzahl	44	22	66
		% innerhalb von Pankreaskopfresektion?	66,7%	33,3%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	4,125[a]	1	,042		
Kontinuitätskorrektur[b]	3,077	1	,079		
Likelihood-Quotient	4,036	1	,045		
Exakter Test nach Fisher				,055	,041
Zusammenhang linear-mit-linear	4,063	1	,044		
Anzahl der gültigen Fälle	66				

Fig. 26 Univariate analysis of pancreatic head resections and severe complications (p=n.s.)

4.9.5 Severe complications and distal pancreatectomy

Similar to pancreatic head resections there was no statistically significant difference of the number of severe complications when a distal pancreatectomy was performed. Furthermore, there was no trend towards a higher rate of complications since this was the less extensive procedure. (p=n.s.) Figure 27

Pankreasschwanzresektion? * Schwere Komplikationen? Kreuztabelle

			Schwere Komplikationen?		
			nein	ja	Gesamt
Pankreasschwanzresektion?	nein	Anzahl	21	15	36
		% innerhalb von Pankreasschwanzresektion?	58,3%	41,7%	100,0%
	ja	Anzahl	23	7	30
		% innerhalb von Pankreasschwanzresektion?	76,7%	23,3%	100,0%
Gesamt		Anzahl	44	22	66
		% innerhalb von Pankreasschwanzresektion?	66,7%	33,3%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	2,475[a]	1	,116		
Kontinuitätskorrektur[b]	1,719	1	,190		
Likelihood-Quotient	2,522	1	,112		
Exakter Test nach Fisher				,189	,094
Zusammenhang linear-mit-linear	2,438	1	,118		
Anzahl der gültigen Fälle	66				

Fig. 27 Univariate analysis of distal pancreatectomy and severe complications (p=n.s.)

4.9.6 Severe complications and the resection margin

The histopathology reports were next to be analyzed. First issue was to examine the impact of the resection margin on the appearance of severe complications. The univariate analysis showed no influence of tumor free resection margins on the frequency of severe complications. (p=n.s.) Figure 28

R-Status * Schwere Komplikationen? Kreuztabelle

			Schwere Komplikationen?		
			nein	ja	Gesamt
R-Status	R0	Anzahl	36	19	55
		% innerhalb von R-Status	65,5%	34,5%	100,0%
	R1	Anzahl	8	3	11
		% innerhalb von R-Status	72,7%	27,3%	100,0%
Gesamt		Anzahl	44	22	66
		% innerhalb von R-Status	66,7%	33,3%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	,218[a]	1	,640		
Kontinuitätskorrektur[b]	,014	1	,907		
Likelihood-Quotient	,224	1	,636		
Exakter Test nach Fisher				,739	,465
Zusammenhang linear-mit-linear	,215	1	,643		
Anzahl der gültigen Fälle	66				

Fig. 28 Univariate analysis of the resection margin and severe complications (p=n.s.)

4.9.7 Severe complications and metastases

Another question to be answered was if the presence of distant metastases had an influence on the morbidity in our cohort. There was no significant difference if the patients suffered of distant metastases or not. (p=n.s.) Figure 29

Schwere Komplikationen? * M-Status Kreuztabelle

			M-Status		
			M0	M1	Gesamt
Schwere Komplikationen?	nein	Anzahl	35	9	44
		% innerhalb von M-Status	67,3%	64,3%	66,7%
	ja	Anzahl	17	5	22
		% innerhalb von M-Status	32,7%	35,7%	33,3%
Gesamt		Anzahl	52	14	66
		% innerhalb von M-Status	100,0%	100,0%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	,045[a]	1	,831		
Kontinuitätskorrektur[b]	,000	1	1,000		
Likelihood-Quotient	,045	1	,832		
Exakter Test nach Fisher				1,000	,534
Zusammenhang linear-mit-linear	,045	1	,833		
Anzahl der gültigen Fälle	66				

Fig. 29 Univariate analysis of the presence of metastases and severe complications (p=n.s.)

4.9.8 Severe complications and lymph nodes

The last issue to be analyzed was the impact of positive lymph nodes on the appearance of severe complications. Again there was no statistically significant difference in the frequency of severe complications no matter if there were negative or positive lymph nodes resected. (p=n.s.) Figure 30

N-Status * Schwere Komplikationen? Kreuztabelle

			Schwere Komplikationen?		
			nein	ja	Gesamt
N-Status	N0	Anzahl	22	14	36
		% innerhalb von N-Status	61,1%	38,9%	100,0%
	N1	Anzahl	13	5	18
		% innerhalb von N-Status	72,2%	27,8%	100,0%
Gesamt		Anzahl	35	19	54
		% innerhalb von N-Status	64,8%	35,2%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	,650[a]	1	,420		
Kontinuitätskorrektur[b]	,254	1	,614		
Likelihood-Quotient	,663	1	,415		
Exakter Test nach Fisher				,550	,310
Zusammenhang linear-mit-linear	,638	1	,425		
Anzahl der gültigen Fälle	54				

Fig. 30 Univariate analysis of negative or positive lymph nodes and severe complications (p=n.s.)

4.10 Univariate analysis of re-operations

As mentioned above, six patients (9,1 %) required at least one re-operation due to a complication. Therefore, risk factors for re-operations were evaluated in an univariate way.

4.10.1 Re-operation and operation time

In the first analysis the probability to be re-operated in regard to the operation time was investigated. The operation time seems to correlate with complications, however, this finding was not statistically significant. The rate of re-operations in turn was more frequent in the group of patients with longer primary operation times. This difference was statistically significant. (p<0,05) Figure 31

OP Dauer ueber Median? * Revisionen Kreuztabelle

			Revisionen		
			nein	ja	Gesamt
OP Dauer ueber Median?	nein	Anzahl	32	1	33
		% innerhalb von OP Dauer ueber Median?	97,0%	3,0%	100,0%
	ja	Anzahl	25	8	33
		% innerhalb von OP Dauer ueber Median?	75,8%	24,2%	100,0%
Gesamt		Anzahl	57	9	66
		% innerhalb von OP Dauer ueber Median?	86,4%	13,6%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	6,304[a]	1	,012		
Kontinuitätskorrektur[b]	4,632	1	,031		
Likelihood-Quotient	7,059	1	,008		
Exakter Test nach Fisher				,027	,013
Zusammenhang linear-mit-linear	6,209	1	,013		
Anzahl der gültigen Fälle	66				

Fig. 31 Univariate analysis of operation time and the probability of re-operation (p<0,05)

4.10.2 Re-operation and age

Secondly the influence of the patient's age on the rate of re-operations was tested. The univariate Chi-square test showed that there is no statistically significant influence of the patient's age. (p=n.s.) Figure 32

Alter ueber dem Median? * Revisionen Kreuztabelle

			Revisionen		
			nein	ja	Gesamt
Alter ueber dem Median?	nein	Anzahl	31	2	33
		% innerhalb von Alter ueber dem Median?	93,9%	6,1%	100,0%
	ja	Anzahl	26	7	33
		% innerhalb von Alter ueber dem Median?	78,8%	21,2%	100,0%
Gesamt		Anzahl	57	9	66
		% innerhalb von Alter ueber dem Median?	86,4%	13,6%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	3,216[a]	1	,073		
Kontinuitätskorrektur[b]	2,058	1	,151		
Likelihood-Quotient	3,381	1	,066		
Exakter Test nach Fisher				,149	,074
Zusammenhang linear-mit-linear	3,168	1	,075		
Anzahl der gültigen Fälle	66				

Fig. 32 Univariate analysis of age and the probability of re-operation (p=n.s.)

4.10.3 Re-operation and pancreatic head resection

The different surgical approaches were investigated next. Again only the two most common resection strategies (pancreatic head resection and distal pancreatectomy) were explored.

Patients who underwent a pancreatic head resection did not have a higher risk of a re-operation. (p=n.s.) Figure 33

Pankreaskopfresektion? * Revisionen Kreuztabelle

			Revisionen		
			nein	ja	Gesamt
Pankreaskopfresektion?	nein	Anzahl	40	4	44
		% innerhalb von Pankreaskopfresektion?	90,9%	9,1%	100,0%
	ja	Anzahl	17	5	22
		% innerhalb von Pankreaskopfresektion?	77,3%	22,7%	100,0%
Gesamt		Anzahl	57	9	66
		% innerhalb von Pankreaskopfresektion?	86,4%	13,6%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	2,316[a]	1	,128		
Kontinuitätskorrektur[b]	1,303	1	,254		
Likelihood-Quotient	2,186	1	,139		
Exakter Test nach Fisher				,147	,128
Zusammenhang linear-mit-linear	2,281	1	,131		
Anzahl der gültigen Fälle	66				

Fig. 33 Univariate analysis of pancreatic head resection and the probability of re-operation (p=n.s.)

4.10.4 Re-operation and distal pancreatectomy

Lastly the group of distal pancreatectomies was topic of the univariate analysis. Comparable to the group of pancreatic head resections the distal pancreatectomy group did not show a higher rate of re-operations. (p=n.s.) Figure 34

Pankreasschwanzresektion? * Revisionen Kreuztabelle

			Revisionen		
			nein	ja	Gesamt
Pankreasschwanzresektion?	nein	Anzahl	30	6	36
		% innerhalb von Pankreasschwanzresektion?	83,3%	16,7%	100,0%
	ja	Anzahl	27	3	30
		% innerhalb von Pankreasschwanzresektion?	90,0%	10,0%	100,0%
Gesamt		Anzahl	57	9	66
		% innerhalb von Pankreasschwanzresektion?	86,4%	13,6%	100,0%

Chi-Quadrat-Tests

	Wert	df	Asymptotische Signifikanz (2-seitig)	Exakte Signifikanz (2-seitig)	Exakte Signifikanz (1-seitig)
Chi-Quadrat nach Pearson	,618[a]	1	,432		
Kontinuitätskorrektur[b]	,181	1	,670		
Likelihood-Quotient	,631	1	,427		
Exakter Test nach Fisher				,494	,339
Zusammenhang linear-mit-linear	,608	1	,435		
Anzahl der gültigen Fälle	66				

Fig. 34 Univariate analysis of distal pancreatectomy and the probability of re-operation (p=n.s.)

4.11 Multivariate analysis of risk factors for survival

After univariate analyses independent risk factors for survival had to be identified. Therefore risk factors, which showed a p-value <0,20 in Fisher's t-test in the univariate analysis, were further studied in a multivariate analysis. Variables, which fulfilled these criteria, were m-status, r-status, g-status, operation time and pancreatic head resection.

Cox multivariate regression analysis showed that the presence of distant metastases at the time of operation was an independent risk factor. This was the most powerful factor to

influence overall survival with a Hazard ratio of 4,72 (CI95%: 1,95 – 11,39). Furthermore, the grading of the tumor and the resection margins could also be identified as significant prognostic relevant. Nonetheless, the duration of the operation and a pancreatic head resection were no independent risk factors. Figure 35

	B	SE	Wald	df	Signifikanz	Exp(B)	95,0% Konfidenzinterv. für Exp(B)	
							Untere	Obere
mstatus	1,551	,450	11,890	1	,001	4,715	1,953	11,385
rstatus	1,075	,505	4,543	1	,033	2,931	1,090	7,879
gstatus	,752	,290	6,705	1	,010	2,120	1,200	3,746
OPDauermedia	,390	,460	,719	1	,397	1,477	,599	3,642
Pankreaskopf	,682	,484	1,985	1	,159	1,979	,766	5,112

Fig. 35 Cox multivariate regression analysis of independent risk factors for survival

4.12 Multivariate analysis of the risk of severe complications

Subsequently, a multivariate analysis of risk factors for severe complications was conducted to test risk factors of the univariate analysis. Again only risk factors with a p-value <0,20 in Fisher's t-test were considered, therefore, operation time and the type of surgery (pancreatic head resection or distal pancreatectomy) were evaluated.

In the multivariate analysis no independent risk factor for the incidence of severe complications could be identified. Figure 35

		Regressionskoeffizient B	Standardfehler	Wald	df	Sig.	Exp(B)	95% Konfidenzintervall für EXP(B)	
								Unterer Wert	Oberer Wert
Schritt 1[a]	OPDauermedia	,941	,571	2,722	1	,099	2,563	,838	7,842
	Pankreaskopf	,718	,753	,910	1	,340	2,051	,469	8,966
	Pankreasschwanz	-,257	,748	,118	1	,731	,773	,178	3,354
	Konstante	-1,365	,675	4,088	1	,043	,255		

Fig. 36 Multivariate analysis of independent risk factors for the incidence of severe complications

4.13 Multivariate analysis of risk factors for re-operation

Only one statistically significant risk factor for the probability of a re-operation could be identified in the univariate analysis. This single risk factor was the operation time. For the multivariate analysis again all risk factors which had a p-value <0,20 in Fisher's t-test were analyzed. Hence, the operation time, if a pancreatic head resection was carried out and the age of the patient were studied.

The multivariate analysis confirmed the duration of the operation as an independent risk factor for the rate of re-operations. The longer the primary operation took, the more probable was a subsequent re-operation in the analyzed cohort. The risk to get re-operated was increased 9,48 times in this case (CI95%: 1,05 – 85,51; p<0,05). The remaining two analyzed variables (median age, pancreatic head resection) were statistically not significant in the multivariate setting. Figure 37

		Regressionskoeffizient B	Standardfehler	Wald	df	Sig.	Exp(B)	95% Konfidenzintervall für EXP(B)	
								Unterer Wert	Oberer Wert
Schritt 1[a]	OPDauermedia	2,249	1,122	4,016	1	,045	9,478	1,051	85,508
	altermedia	1,507	,887	2,886	1	,089	4,511	,793	25,654
	Pankreaskopf	,675	,799	,714	1	,398	1,964	,411	9,394
	Konstante	-4,646	1,286	13,046	1	,000	,010		

Fig. 37 Multivariate analysis of independent risk factors for the probability of a re-operation

5 Discussion

Neuroendocrine tumors are rare neoplasm but the incidence is increasing [11]. Over the last years different therapy strategies were evaluated. Nonetheless, surgery is still the gold standard if applicable since the only chance of cure is complete tumor resection [140, 141]. It is universally accepted to perform surgery in a metastasized setting, either to alleviate symptoms due to a functional pNET or to reduce the tumor burden. Patients benefit most if the primary tumor and the metastases are resected similarly [142]. Resection and/or RFA of liver metastases could improve 5-year survival from 25% up to 72% compared to patients whose liver metastases were treated not surgical [143].

Since resection of the tumor is the only chance of cure and pNETs show a low proliferation rate, more aggressive approaches are feasible when compared to adenocarcinoma of the pancreas. pNETs are slow growing tumors and therefore survival rates are good even for metastasized tumors. To control hepatic metastases systemic therapy or liver directed therapies like TACE or selective internal radiation therapy (SIRT) are well-established procedures. Hence, a multidisciplinary approach leads to satisfactory survival rates.

5.1 Reflecting the "official" line regarding various risk factors

The introduction of the ENETS guidelines in 2006 and with it the implementation of the proliferation marker Ki-67 was very useful to optimize the individual therapy [4, 5]. Therefore we favor the ENETS TNM staging. Different publications demonstrated inferior survival rates for patients with G3 tumors [144, 145], hence, G3 tumors were underrepresented in our cohort (n=6, 9,1 %). According to the literature the outcome of the analyzed patients differed depending on whether a patient suffered of a G1 or G2 or G3 tumor. We showed a 5-year survival rate of 75 % (G1) vs. 63 % (G2) vs. 16 % (G3). These findings were in direct correlation with international publications on this topic and G3 pNETs should be regarded as different tumors than G1 pNETs. The differences between G1 and G2 were not huge and within the first three years almost the same.

An important point of criticism of the ENETS classification system is the prognostic value of the grading system. Currently a tumor is classified as G1 when Ki-67 index is below 2 %, G2 tumors have a Ki-67 index of 2 – 20 % and tumors with higher Ki-67 levels are classified as G3 tumors with the worst prognosis. Scarpa et al. propagate a modification of the cut-off levels of Ki-67 index for the three groups. In their study with more than 250 patients suffering of pNET they introduced their modified tumor grading with cut-offs at 5 and 20 %, which

showed to be prognostic relevant [87]. Unfortunately, we do not have a Ki-67 immunohistochemistry of every specimen and therefore we could not verify these findings. Nonetheless, we set off a prospective study including every type of gastroenteropancreatic neuroendocrine tumor, which among other things will focus on different cut-off levels of Ki-67 index.

Internationally there is almost no doubt about the benefit of the Ki-67 index, however, there are contradictory reports on other risk factors.

An obstacle to prove a particular variable as an independent risk factor is often complicated due to the fact that analyzed groups are small. In our cohort with 66 patients we could not demonstrate if either UICC or ENETS classification system is prognostic relevant, however, this is one of the bigger single center cohorts. The median overall survival of the different groups was scattered widely and no conclusion could be drawn out of these two classification systems. Nonetheless, we were able to state that group IV had the worst overall survival, however, there was no significant difference within the other groups (Figure 38). This is most likely because of the few patients in every group. Hence, this should not lead to the misinterpretation that either classification is inapplicable and these findings are concordant to other publications [84].

However, there are also studies, which show a correlation of survival rates and classification systems [144, 146]. Sellner et al. saw a prognostic relevance of TNM categories in their investigated population. Not unexpected showed group IV the worst outcome. The median follow up time was 57 months (2 – 240 months) and only 18 patients were analyzed [144]. Therefore, the main problem of the practicability of both classification systems is the plethora of different groups in combination with too little patients investigated in a single study.

GROUP	A	B	C
I	57,495	45,876	69,114
IIA	98,556	72,182	124,929
IIB	85,057	57,505	112,609
IIIB	149,983	87,21	212,757
IV	48,827	29,896	67,758

Fig. 38 Calculated median overall survival (months) of the ENETS classification system (group I – IV). A: calculated median overall survival. B: CI95% minimum. C: CI 95% maximum.

5.2 Size does matter

Another important issue, which is internationally discussed controversially, is the surgical approach concomitant with the oncologic radicalness. As mentioned above Ki-67 index is an independent risk factor and determines in a way the surgical approach. An enucleation of an insulinoma is not even widely accepted, the organ sparing procedure is demanded. However, the discrepant positions are obvious when the eligible surgical radicalness should be determined for tumors of 2 – 4 centimeters. If Ki-67 index is known the discrepancy shrinks.

Concordant to many other studies we could show that tumor size is not an independent prognostic factor (Figure 9). However, we saw that tumor size influences the probability of lymph node metastases. The chance of positive lymph nodes correlated with the size of the resected tumor. Patients with a T4 tumor had in 66,67 % lymph node metastases, but, T1 tumors had only a risk of 8,33 % of positive lymph nodes ($p<0,05$). Enucleations were excluded in this calculation since no lymph nodes were resected via this approach.

Nonetheless, we demonstrated that lymph node metastases did not influence the overall survival (Figure 10). This point is discussed very controversially with a majority sympathizing with our views [84, 109, 141, 144, 147]. Bilimoria et al. who analyzed over 3500 patients with pNET lymph node metastases were a significant prognostic factor on univariate analysis, but not on multivariate analysis [148]. Therefore, an aggressive surgical strategy should be considered in patients with tumors > 2 cm.

Furthermore, an aggressive surgical approach in patients with tumors > 2 cm is confirmed by the fact that tumor size correlates with the presence of distant metastases. We have seen distant metastases in 5,26 % in patients with T1 tumors and this rate increases almost threefold if a patient suffers of a T2 tumor (15,29 %). Most distant metastases were seen in patients with T4 tumors (57,14 %).

Casadei and coworkers showed in a study that enucleation can be performed safely in patients with tumors up to 4 cm. Their analysis included 46 patients of which 15 underwent enucleation and there was no difference in the overall survival. The title of the study might be misleading since the mean tumor size was 1,9 cm (+/- 0,8) in the enucleation group. Enucleation was more frequently used in patients with functioning tumors [149].

When enucleation is performed a proper lymphadenectomy is not usually done. This is in fact no disadvantage for the patients because most enucleated tumors are benign functioning tumors like insulinomas or smaller than 2 cm. However, we could demonstrate that the rate of distant metastases is higher in patients who also have lymph node metastases. Patients with positive lymph nodes showed in 38,89 % distant metastases, whereas N0 patients suffered in 19,44 % of distant metastases.

The presence of distant metastases is an independent prognostic factor for the overall survival in our group. A Hazard ratio of 4,72 (CI95%: 1,95 – 11,39) was seen in patients with metastases, which led to a 472 % greater risk to decease earlier (p<0,05) (Figure 34). Hence, an enucleation of a tumor exceeding 2 cm should be performed only if a complete preoperative workup was done and Ki-67 index should be known. Moreover, the higher probability of lymph node metastases associated with pNETs bigger than 2 cm carries the risk of recurrent disease if no lymph nodes were resected.

5.3 Prognostic relevance

As mentioned above there are several factors influencing overall survival. Tumor size and lymph node metastases were two examples to illustrate dissent in international publications. One of the main problems might be the lack of statistical power of many studies. pNETs are a rare entity, hence single center experiences are not always including a lot of patients. There are publications with only 18 or 22 patients but even postulating significant findings [144, 150]. Another problem are the differences within the study population in regard to treatment and follow up periods vary significantly between studies.

However, we presented the presence of distant metastases as an independent risk factor (Figure 34). Although, there are several publications in which distant metastases were not of prognostic relevance [84, 109], but, the majority supports our hypothesis [83, 146, 151]. The median survival of a patient with distant metastases was 48,83 months (CI95%: 29,9 – 67,76 months) compared to 150,23 months (CI95%: 120,08 – 180,39 months) in patients without metastases (p<0,05). Nonetheless, stage IV patients benefit from an aggressive surgical approach compared to those not operated [152, 153]. In regard to pNETs the indicator of advanced malignancy, like lymph node or liver metastases, should be re-evaluated. Hence, patients with liver metastases should be considered for surgery as well.

There are also divergent positions on the influence of tumor free resection margins. Proponents of the unimportance of tumor free resection margins may argue that this rate is anyway overestimated, since there is evidence that standardization of histologic screening increases that rate of tumor infiltrated resection margins after pancreatic surgery [154]. It is not remarkable that investigators do not ascribe importance to resection margins when even debulking operations lead to a survival benefit. Nonetheless, there are different findings as well [141] and in our study local tumor control was also an independent risk factor. Cox multivariate regression analysis revealed the resection margin as prognostic relevant with a median survival rate of 152,07 months (CI95 %: 123,74 – 180,4 months) in patients with

tumor free resection margins (Figure 34). Patients with a R1 situation had a median survival rate of 51,65 months (CI95%: 28,09 – 75,2 months) (p<0,05).

We analyzed further variables for their prognostic relevance for the overall survival. Sex and age of the patient or the surgical approach (pancreatic head resection or distal pancreatectomy) were no independent risk factors. These findings are concordant to other publications. Nonetheless, working groups published unique relevant prognostic factors like location of the tumor [145] or functional status of the tumor [155] or association of MEN-1 [151]. In accordance with this "tradition" we introduce the operation time as a risk factor (Figure 20). In our patients the calculated median overall survival was 163,63 months (CI95%: 129,73 – 197,52 months) if the median operation time was not exceeded. This rate decreased to 70,26 months (CI95%: 53,8 – 86,73 months) when the operation took longer than the median duration of 192,5 minutes (p<0,05). However, this effect was only statistically significant in univariate analysis.

5.4 Morbidity and mortality

The overall complication rate in our series came to 30,77 %. This rate is concordant to other studies and ranges in the middle of published results. Furthermore, the rates of 30-day mortality and of re-operations were comparable to international study groups [84, 109, 145].

The multivariate analysis did not revealed any risk factor for the occurrence of a complication. Analysis included operation time, sex, age of patients, surgical strategy and TNM (Figure 35). Pancreatic fistula was seen in 13 patients (19,7 %) and five patients required an interventional drainage (ISGPS B). A possible explanation of pancreatic fistulas might be that the pancreas of a patient with pNET is generally soft, making the anastomosis challenging. We have seen three patients with an insufficiency of the pancreaticojejunostomy, one requiring re-operation. Unfortunately this patient died due to postoperative complications.

In total we have lost three patients within 30 days, whereby one patient died because of a heart failure but two deaths were directly related to surgery. Hence, our 30-day mortality rate was 4,5 %.

Six patients (9,1 %) of the investigated cohort had to be re-operated because of a specific complication. All re-operations were necessary due to anastomotic leakage and insufficiency of the hepaticojejunostomy was in four cases the indication for the re-operation. Neither the surgical strategy (pancreatic head resection or distal pancreatectomy) nor the age of the

patient did influence the probability of re-operations. However, in the multivariate analysis the duration of the primary operation was an independent risk factor to get re-operated (Figure 36) ($p<0,05$).

Therefore, we suggest that pancreatic resection for pNETs is safe but surgery should be performed in a high-volume center. Treatment of pNETs should always be multi-disciplinary due to the rarity and different manifestations of the disease. A primarily palliative setting may be converted with liver directed therapy or systemic treatment to a resectable tumor burden. Moreover, an answer to the controversial discussion of risk factors is only possible with a large study population to gain statistical power. High-volume centers can initiate clinical trials in cooperation either with other centers and/or with the various medical departments involved in the treatment of pNETs.

5.5 Limitations

We could present a study of 66 consecutive patients with pNETs who all underwent tumor resection. Nonetheless, this is a heterogenic population including functional active and inactive as well as benign and malignant tumors. Within the 15 years of recruiting the understanding of this tumor entity has changed and surgical techniques along with treatment strategies have improved. We have included only patients whose tumor was resected which in turn led to a bias. Furthermore, the follow up period started with the date of the operation. We did not take account into the time period between diagnosis and surgery or tumor directed therapy previous to surgery. This may have influenced our results and overall survival rates negatively. Commonly to almost every study a limitation of our study is its lack of statistical power because of a small cohort and impossibility of subgroup analysis therein.

Due to the rarity of pNETs our study population is comparable to other published single center experiences. The size of our group is in the upper quarter of published studies. Another advantage is the completeness of data with only one patient lost for follow up. We analyzed only patients whose primary tumor was resected, hence we have a very uniform population. Moreover, we could verify already published results and even present new relevant factors in multivariate analyses. Nevertheless, there have studies been published in which only univariate analyses were performed.

6 Abstract

Introduction.

Neuroendocrine tumors of the pancreas (pNET) are rare neoplasms, although the incidence is rising. pNETs may get symptomatic due to secreted peptides (diarrhea, hypoglycemia) or may be functionally inactive. Aim of this study was to assess morbidity and mortality and to discover risk factors of all resected pNETs at our institute.

Methods.

With a retrospective analysis we studied the data of patients who got operated because of a pNET from 1996 to 2011. One inclusion criterion was that the primary tumor has to be resected, therefore we have no patients included who had undergone only a explorative laparotomy. Minimal follow up time was 12 months. Besides demographic data we also evaluated prognostic relevant parameters for morbidity, mortality and overall survival.

Results.

From 1996 to 2011 66 patients (33 female, 33 male) were operated because of a pNET. A distal pancreatectomy was done commonest (n=30), followed by 22 pancreatic head resections. Pancreatectomy had to be done in 5 patients and a segmental resection was feasible in 9 patients. The majority of patients had a G1 or G2 tumor (n=60, 90,91 %) and 14 patients (21,21 %) suffered from distant metastases at the time of operation. We could demonstrate that the grading, the presence of metastases and the resection margins had a significant influence on the overall survival. However, lymph node metastases, the surgical approach or the operation time did not have prognostic relevance. Pancreatic fistula was seen in 13 patients (19,7 %) and five patients required an interventional drainage (ISGPS B). An insufficiency of the pancreaticojejunostomy was detected in 3 patients. Six patients (9,1 %) had to be re-operated due to a complication. The multivariate analysis did not reveal any risk factor to develop a complication. However, we could demonstrate that the duration of the primary operation had a significant influence on the rate of re-operations. The calculated mean overall survival was 130,17 months (CI95%: 103,21 – 157,14 months) with a calculated 5-year survival of 66 %. The 30-day mortality was 4,5 % (n=3).

Discussion.

International working groups are divided on risk factors, however, we could demonstrate that metastases, grading and resection margins significantly influence survival. These findings are mainly concordant with the majority of other publications. Due to the rarity of these tumors treatment should be done in a center in a multidisciplinary setting and surgery can be done with an acceptable morbidity and mortality.

7 Zusammenfassung

Einleitung.

Neuroendokrine Tumore des Pankreas (pNET) sind seltene Tumore, wenngleich ihre Inzidenz steigt. pNETs können symptomatisch werden wenn sie Peptide sezernieren (Diarrhoe, Hypoglykämie) oder sie bleiben funktionell inaktiv. Ziel dieser Studie war es, die Morbidität, Mortalität und Risikofaktoren hierfür aller an unserem Zentrum operierten Patienten mit einem pNET zu erfassen.

Material und Methoden.

In einer retrospektiven Analyse haben wir alle Daten von Patienten, die aufgrund eines pNET zwischen 1996 und 2011 operiert wurden, ausgewertet. Es sind in dieser Studie nur Patienten deren Tumor reseziert wurden enthalten, das heißt Patienten, die eine explorative Laparotomie erhalten haben, sind exkludiert. Die minimale Nachverfolgungszeit beträgt 12 Monate. Neben demographischen Daten wurden auch prognostisch relevante Parameter für Morbidität, Mortalität und das Gesamtüberleben evaluiert.

Resultate

Zwischen 1996 und 2011 wurden 66 Patienten (33 weibliche, 33 männliche) mit einem pNET operiert. Eine Pankreaslinksresektion war die häufigste Operation (n=30), gefolgt von einer Pankreaskopfresektion (n=22). Eine Pankreatektomie wurde bei fünf Patienten und eine segmentale Resektion bei neun Patienten durchgeführt. Der Großteil der Patienten hatte zum Operationszeitpunkt einen G1 oder G2 Tumor (n=60; 90,91 %), 14 Patienten (21,21 %) einen G3 Tumor. Wir konnten zeigen, dass das Tumorgrading, das Vorhandensein von Fernmetastasen und das Erreichen einer R0-Resektion einen signifikanten Einfluss auf das Gesamtüberleben haben. Lymphknotenmetastasen, die Resektionsstrategie oder die Operationszeit hatten jedoch keine prognostische Relevanz. Eine Pankreasfistel trat bei 13 Patienten (19,7 %) auf und fünf Patienten benötigten eine interventionelle Drainage (ISGPS B). Eine Insuffizienz der Pankreatikojejunostomie erlitten drei Patienten. Sechs Patienten mussten (9,1 %) aufgrund einer Komplikation revidiert werden. In der multivariaten Analyse konnte kein Risikofaktor für das Auftreten postoperativer Komplikationen ermittelt werden. Die Dauer der primären Operation hatte allerdings einen direkten Einfluss auf die Rate der Revisionen. Das kalkulierte mediane Überleben betrug 130,17 Monate (CI95%: 103,21 – 157,14 Monate) mit einem kalkulierten 5-Jahres Überleben von 66 %. Die 30-Tages Mortalität beläuft sich auf 4,5 % (n=3).

Diskussion.

Die internationalen Publikationen sind widersprüchlich in Bezug auf die Risikofaktoren. Wir

konnten jedoch darlegen, dass Fernmetastasen, das Grading sowie eine R0-Situtation das Überleben signifikant beeinflussen. Trotz der Widersprüche decken sich unsere Beobachtungen mit dem Großteil der publizierten Studien. Aufgrund der Seltenheit dieser Tumorentität sollte eine Behandlung in einem Zentrum mit einem interdisziplinären Ansatz erfolgen. Auch ausgedehnte Resektionen können mit vertretbarer Morbidität und Mortalität durchgeführt werden.

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9 Eidesstattliche Versicherung

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

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selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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München, 01.06.2015

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