Complex clinical evaluation of pancreatic cancer

The role of registries in data analysis of malignant diseases

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Table of contents

List of abbreviations

AJCC - American Joint Committee on Cancer

BMI - body mass index

CP - chronic pancreatitis

CR – complete regression

CT – computed tomography

ECOG - Eastern Cooperative Oncology Group

EPI - exocrine pancreatic insufficiency

ERCP - endoscopic retrograde cholangiopancreatography

EUS – endoscopic ultrasound

FNA – fine needle aspiration

G-CSF - granulocyte colony-stimulating factor

HPSG – Hungarian Pancreatic Study Group

MRI - magnetic resonance imaging

IGF-1R - Insulin-like growth factor-1 receptor

IRE - irreversible electroporation

LAPC - locally advanced pancreatic cancer

NCCN - National Comprehensive Cancer Network

OS – overall survival

PC- pancreatic cancer

PFS – progression free survival

PET - positron emission tomography

PD – progressive disease

PNET - pancreatic neuroendocrine tumor

PR – partial regression

RFA - radiofrequency ablation

RPP - Registry for Pancreatic Patients

SD – stable disease

UICC - Union for International Cancer Control

1. Introduction

Pancreatic cancer (PC) is one of the most aggressive types of human malignancies and to present it remains a major health problem. PC is a relatively rare type of tumor, but due to its high mortality rate it is one of the most frequent causes of cancer death in the world. The number of patients with PC is increasing globally. Data suggest that the onco-epidemiological situation related to pancreatic cancer in Central European countries is even worse compared to that in the Western world.

There is a wide variation in the incidence of PC around the world, suggesting that environmental factors are important in the pathogenesis. Smoking is a major known risk factor for pancreatic cancer, while dietary factors seem to be less important. The role of other environmental and lifestyle factors is less discovered. Other possible risk factors include chronic pancreatitis, obesity and type 2 diabetes.

The management of PC remains a big challenge. There are no screening tests for early detection of PC. Because of the late presentation of the disease, less than 15% of patients can be offered a potential curative treatment by the time of diagnosis and up to 30% of the patients die within 12 months.[1] Although new treatment options have become available for the treatment of PC during the last years, the treatment of advanced disease is still not resolved. For selected patients neoadjuvant therapy offers the potential for tumor downstaging and in patients with resectable disease, adjuvant chemotherapy allows to improve the five-year survival rate. In metastatic cancer the FOLFIRINOX regimen and the use of nab-paclitaxel have recently shown survival benefit compared to gemcitabine chemotherapy, which was the main therapeutic option for more than 10 years.[2,3] In contrast, the role of FOLFIRINOX in borderline resectable disease and locally advanced pancreatic cancer (LAPC) is a question of debate. The role of radiotherapy in the management of PC is also a controversial.

There is only limited information available on the management of PC from Central Europe including Hungary. In order to improve outcome of PC, it is essential to determine which factors contribute to the unfavorable trends seen in less developed countries.

2. Descriptive epidemiology

The number of cases with PC is increasing worldwide. It is the eighth leading cause of cancer deaths in males and the ninth in females.[4] In 2012 there were 103.773 newly diagnosed

cases and 104.463 fatal outcomes in Europe.[5] It is estimated that by the year of 2017 the number of death from PC will exceed the death rate caused by breast cancer in the EU.[6] There are data reporting even higher incidence and mortality rates in Central Europe compared to western countries.[7] The rate of PC in 2012 was highest in the Czech Republic, followed by Slovakia, Armenia and Hungary.[8] An epidemiologic study conducted in Serbia between 1991 and 2010 demonstrated high mortality rates with increasing mortality trend in both genders and in most age groups.[9] The number of new cases was 2,373, while 1,837 died due to PC in Hungary in 2010.[10]

The number of patients diagnosed with the disease is almost identical with the number of deaths caused by PC, which reflects the aggressiveness of the malignancy. Mortality varies largely in different areas of the world. High PC mortality rates were reported in Northern America (6.9/100,000 people) and Western Europe (6.8/100,000 people), while mortality was lowest in Middle Africa and South Central Asia in 2012.[8] The rate of mortality in males was highest in Central and Eastern Europe (Latvia and Hungary: 11.9/100,000 and 11.5/100,000 people respectively) in 2012.

Pancreatic cancer is known to affect older individuals, less than 10% of patients with PC are below the age of 50.[11] However, the incidence rises sharply after the age of 45 years. The median age at diagnosis is 71 years in the US.[12] There are differences by sex and race in the incidence and mortality of the disease.[13] PC is more common in men than women (1.3:1) and in blacks than in whites (14.8/100,000 in black males vs. 8.8/100,000 in the general population).[14] Mortality of PC increases with age in both genders.

3. Risk factors

3.1. Hereditary risk factors

Familial accumulation of PC has been observed in some families. The risk of inherited disease is almost doubled if someone has two first-degree relatives with PC.[15] Family history is present in approximately 5 to 10 percent of PC patients.[16] The specific molecular background of familial PC has not been identified yet.

Genetic susceptibility loci such as BRCA2, PALB2, CDKN2a and ATM have been intensively studied in relation to the risk of PC.[17] KRAS mutation was found to be relatively common, especially in the early phase of the development of PC. In later stages P53, STAT3,

SMAD4 and ARF/INK4 are involved in the carcinogenic process. Beside its role in cell proliferation, differentiation and apoptosis, the overexpression of insulin-like growth factor-1 receptor (IGF-1R) has been associated with chemoresistance in PC.[18]

There are six hereditary syndromes in association with PC. Patients with such a condition are considered to have high risk of developing PC and other malignancies (**Table 1**.).

multiple endocrine neoplasia type 1 (MEN1)
hereditary nonpolyposis colon cancer (Lynch syndrome)
von Hippel-Lindau syndrome
Peutz Jeghers syndrome
hereditary breast/ovarian cancer syndrome
familial atypical multiple mole melanoma (FAMMM) syndrome

Table 1. Hereditary syndromes associated with high risk of PC

The association of ABO blood group as an inherited factor and the risk of PC has been observed in two large prospective cohort studies.[19] Belonging to a non-O blood group (type A, AB, or B) represents a higher susceptibility to develop PC. More data is needed to confirm these findings and to determine the underlying mechanism of the link between ABO blood and the risk of PC.

3.2 Non-hereditary risk factors

There is a wide variation in the incidence of PC around the world, suggesting that environmental factors are important in the pathogenesis.

3.2.1. Chronic pancreatitis

Lowenfels et al found that the risk of PC is elevated in patients having chronic pancreatitis (CP).[20] Long term inflammation of the pancreatic tissue is supposed to be associated with genomic damage leading to cell proliferation and activation of the carcinogenic process. However, a recent analysis of 10 case-control studies of 5048 PC patients found only a moderate link between chronic pancreatitis and the risk of PC (odds ratio of 2.7).[21] As the incidence of PC among patients having CP is low (less than 5%), it is estimated that only the minority of PC cases could be avoided with effective treatment of CP.[22]

3.2.2. Smoking

Smoking counts as one of the strongest environmental risk factor for PC. There are a number of chemicals in cigarette smoke, at least 60 of them are suspected to cause cancer.

A meta-analysis reported an elevated risk of PC both for current and for former smokers.[23] Parkin et al reported that 26.2% of PC cases in males and 31.0% in females were associated with smoking.[24] Smoking increases the risk of PC by 75% compared to non-smokers and according to the results of the EPIC study passive smoking is associated with an increased PC risk of 50% as well.[25, 26] The amount of cigarette consumption is positively associated with the risk of PC.[27] The cessation of smoking could prevent approximately 27% of PC related deaths however, the risk of developing PC persists for at least 10 years after quitting smoking.[28]

3.2.3. Diabetes mellitus

Over the past decades multiple studies have reported a positive association between diabetes and PC.[29] Hyperglycemia or manifest diabetes is present in 50-80% of patients diagnosed with PC. Both type I and type II diabetes have been shown to increase cancer risk.[30] The underlying mechanism is unclear. Insulin resistance, compensatory hyperinsulinaemia and hyperglycaemia are supposed to promote the carcinogenic process. It has been show that high circulating levels of insulin, HbA1c and C-peptide might elevate the risk of PC.[31]

However, as diabetes could be a manifestation of PC, the link between diabetes and the risk of cancer is a question of debate. New onset diabetes probably should be evaluated in a different manner than the diabetes lasting for more than 3 years. Oral antidiabetics and insulin have been shown to reduce cancer risk however, the etiologic role of diabetes treatment remains controversial.[32] It is also not clear, whether the presence of diabetes affects survival in PC patients.[33]

3.2.4. Alcohol intake

Many studies have been conducted to evaluate the association between alcohol intake and the risk of PC. A possible explanation is that high alcohol consumption can cause chronic pancreatitis. Besides the main metabolite of alcohol, acetaldehyde is a well known carcinogenic factor. According to the results of pooled analyses, moderate alcohol intake seems not have any significant effect, while heavy drinking (>30 grams/day) increases the risk of PC.[34,35] Similar results were seen in a recent systematic review and meta-analysis of

pooled data from prospective cohort studies, especially the consumption of liqueur was found to be highly associated with PC risk.[36]

Conversely, a number of studies do not confirm the relationship between total alcohol intake and development of PC.[37] In summary, due to a lack of convincing evidence the etiologic role of alcohol use regarding to the risk of PC remains unclear.

3.2.5. Excess weight (overweight and obesity)

A link between overweight and obesity and the risk of PC has been suggested. The association has been confirmed in recent large pooled analyses and meta-analyses.[38, 39] The effect of elevated body mass index (BMI) was relatively consistent accross trials, showing a 20-50% increased PC risk among obese patients compared to non-obese people.

High levels of circulating insulin and C-peptide, hyperglycemia and insulin resistance, the effects of the visceral adipose tissue, release and synthesis of hormones, cytokines and chemokines might be important factors with regard to the relationship of obesity and the risk of PC. However, one single mechanism is unlikely to explain the association.

Reported results about the effect of excess weight on PC mortality and survival have been highly inconsistent. Nonetheless, considering the fact that physical inactivity has also been shown to increase PC risk, reducing the prevalence of overweight in the general population might improve incidence and outcome of PC as well.

3.2.6. Diet

Much controversy exists regarding the role of dietary factors in the developement of PC. There is some evidence that „western diet" including high consumption of saturated fat, red or processed meat, high-temperature cooking, may increase the risk of the disease. A recent study conducted in the UK found, that low meat eaters and vegetarians had a significant lower mortality (30-50%) for PC.[40] An association between the intake of processed meat and the incidence of PC has been shown in a meta-analysis of 11 prospective studies.[41] However, not all studies were able to confirm these results.[42]

Several studies, including meta-analyses support the hypothesis that fruit and vegetable intake might be protective against PC. According to the results of a summary review of meta-analytical studies increasing fruit or folate intake were identified as the most important preventive factors.[43]

4. Clinical presentation, diagnosis and staging

Due to the lack of symptoms, early and accurate diagnosis of PC is challenging. By the time of diagnosis, less than 15% of patients can be offered a potential curative treatment. Diagnosis is usually based on clinical presentations, imaging tests, tumor markers and biopsy.

4.1. Clinical presentation

Symptoms and signs are non-specific for PC and appear often in advanced stage. The most frequent presenting symptoms are weight loss, jaundice and pain however, initial presentation may vary according to the localisation of the tumor. Pancretic head tumors – representing 60-70% of the cases – are commonly associated with jaundice, steatorrhea, and weight loss, while tumors of the body or tail usually present usually with abdominal pain radiating to the back. Presenting symptoms are summarized in **Table 2**.

Fatigue	Nausea
Weight loss	Back pain
Asthenia	Vomiting
Anorexia	Diarrhea
Abdominal pain	Steatorrhea
Jaundice	Thrombophlebitis

Table 2. Presenting symptoms of PC

New onset diabetes mellitus may occur in approxiamtely 10% of the patients.[44] Screening of individuals with new onset diabetes is not feasible, due to a very small number of detectable pancreatic tumors.

Due to the production of procoagulant factors thromboembolic events are frequent complications of PC, presenting classically as migratory thrombophlebitis (Trousseau's syndrome).[45] Appearance of thrombosis should always arouse clinical suspicion of malignancy.

In advanced stages symptoms of metastatic disease may be present. Metastases might be localized in the liver, lung or peritoneum. Signs of metastatic dissease include ascites, a palpable abdominal or periumbilical mass or jaundice.

Routine laboratory test might be normal or show nonspecific alterations such as anaemia, elevated serum bilirubin or alkaline phosphatase levels.

4.2. Tumor markers

The value of existing tumor markers such as CA 19-9 and CEA is limited. Currently, there are no screening tests for early detection of PC.

The use of the CA 19-9 tumor marker has been widely accepted in the management of PC. Clinical usefulness of CA 19-9 was reported in early diagnosis, assessment of response to chemotherapy and monitoring progression of PC.[46] The sensitivity and specificity of CA 19—9 for PC in symptomatic patients is 79–81% and 82–90%.[47] CA 19-9 is an isolated Lewis-antigen. In approximately 10% of PC patients the level of CA 19-9 will not be elevated, because they are Lewis-negative.

CEA is a less commonly used biological marker. Besides PC, the level of CEA may be elevated in adenocarcinoma arising from the colon, breast or stomach. CEA can be used for prediction of prognosis of PC, however the sensitivity and specificity of the marker is limited.

4.3. Imaging techniques

4.3.1. Transabdominal ultrasound

Transabdominal untrasound is one of the first tests for a patient presenting with gastrointestinal symptoms. The appearence of PC might be diverse, typically a focal hypoechoic lesion is seen with irregular margins. In case of biliary obstruction dilated bile ducts refer to the presence of a pancreatic tumor. Pancreatic duct cut off, dilatation of the pancreatic duct, parenchymal atrophy and contour abnormalities might also be secondary signs of PC during ultrasound.

In a large prospective cohort of 900 patients the sensitivity of transabdominal ultrasound for detecting PC was 90%.[48] However, there is a reduced sensitivity for detection of tumors ≤2 cm in size.

4.3.2. Computed tomography (CT)

Abdominal CT counts as the primary imaging modality for PC. Multidetector row (MD) CT has the highest sensitivity (89-97%), it’s clinical usefullness in the preoperative diagnosis, staging, treatment planning and follow-up of patients with pancreatic tumor is widely accepted.[49]

PC appears typically as a hypoattenuating mass on CT scan. The accurate characterization of the tumor, it's relationship to adjacent structures, including vascular structures is essential in the management of PC.

Recognition of secondary signs (see above) might bee crucial, as due to the lack of attenuation difference between the cancer and the surrounding tissue, approximately 11% of the tumor lesions are not visible at MDCT.[50]

4.3.3. Magnetic resonance imaging (MRI)

Generally, there is no significant difference between MRI and contrast- enhanced CT regarding sensitivity and specificity. However, MRI may have some advantage in the detection of small pancreatic tumors or characterisation of cystic lesions.[51] The choice of using one or the other technique depends on availability and local institutional practice guidelines.

Magnetic resonance cholangiopancreatography (MRCP) is a useful tool to define the biliary tree and pancreatic duct. The sensitivity of MRCP is similar to endoscopic retrograde cholangiopancreatography (ERCP) in detecting PC, but MRCP is safer, because its non-invasiveness. MRCP is routinely used for the evaluation of the pancreaticobiliary system if ERCP is not feasible (e.g., gastric outlet stenosis, proximal duodenal stenosis, previous surgery: Roux-en Y biliary bypass etc.) or not indicated (i.e., no need for therapeutic intervention).

4.3.4. Endoscopic retrograde cholangiopancreatography (ERCP)

ERCP is not used anymore for diagnostic purposes, but it is frequently used for the palliation of PC-related complications. PC associated morhologic alterations of the biliary tree and pancreatic ducts become visible helping to establish the diagnosis. The sensitivity and specificity of ERCP to detect PC was 70% and 94% respectively.[52] In contrast to other imaging modalities ERCP provides the oppotunity of histological diagnosis using brush cytology, fine needle aspiration (FNA) or forceps biopsy. However, EUS-guided FNA is superior to ERCP in terms of sensitivity of detecting pancreatic malignancy.

In case of biliary obstruction caused by PC endoscopic stent placement during ERCP is a less invasive option for palliation compared to surgical bypass. More details on this issue will be provided below.

4.3.5. Endoscopic ultrasound (EUS)

Since its introducton in the early 1990s EUS has become an essential tool for diagnosis and staging of pancreatobiliary disorders. It has been considered to be especially useful when tumors are small (<2 cm in size) without any visible alteration seen on CT scan. EUS-FNA is an appropriate and safe method for histological confirmation of pancreatic malignancy. Due to it's higher success rate, EUS-FNA has replaced ERCP with brush citology for tissue acquisition. A recent meta-analysis showed, that the pooled sensitivity and specificity of EUS-FNA for making the diagnosis of PC were 86.8% and 95.8% respectively.[53] New techniques, such as contrast-enhanced EUS and EUS elastography are promising methods for further improvement of diagnostic accuracy of PC.

4.3.6. Positron emission tomography (PET CT)

The use of FDG-PET might be indicated in patients with suspected pancreatic malignancy in whom CT and EUS fail to detect a lesion in the pancreas. However, it is more useful for the monitoring of treatment response and detecting disease recurrence. The detection of occult metastases using PET may be helpful to avoid noncurative resection. Sensitivity and specificity rates for the detection of PC of 46%-71% and 63%-100% have been reported.[54]

4.3.7. Pathologic diagnosis

Histologic confirmation is the gold standard procedure for diagnosis of PC. However, not all patients with suspected PC will have a pathological verification. Fit patients with potentially resectable disease do not necessarily need a biopsy before surgery. In contrast, in case of suspected chronic or autoimmune pancreatitis it is recommended to do the preopoerative biopsy, as these conditions tend to mimic PC. False negativity occurs in a certain proportion of cases as well. In elder patients or patients with poor performance status but clear clinical evidence of PC, there is no therapeutic consequence of histologic confirmation. For all kind of reasons, 11.76% of the patients with PC diagnosis in the SEER database did not have a pathologic verification.[55]

The biopsy can be performed using percutaneous FNA with either US or CT guidance. EUS guided biopsy is considered as the best method for histologic confirmation due to its high sensitivity and specifictity and as it is less likely to disseminate tumor cells intraperitoneally. Beside establishing the diagnosis, EUS is a usefull procedure for the staging of PC.

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Table 3. TNM staging system for pancreatic cancer (AJCC/UICC)

4.4. Staging

The most preferred staging system for PC is the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM classification (**Table 3**.).[56] The extent of the disease determines the prognosis and it is essential in treatment planning.

One major goal at initial workup is to identify patients who are eligible for surgical resection with curative intent. However, there is a more practical staging system based on the consensus report of the American Hepato-Pancreato-Biliary Association. Localized disease can be divided into resectable, borderline resectable and unresectable from the surgeons perspective.[57] There are well-defined radiologic criteria for resectablility adopted in the National Comprehensive Cancer Network (NCCN) guidelines, which should be considered before making the decision of neoadjuvant treatment or upfront surgery in PC cases without distant metastases.[58]

4.5. Pancreatic neuroendocrine tumors

Pancreatic neuroendocrine cancer (PNET) originates from the endocrine cells of the pancreas. PNETs are uncommon tumors with increasing incidence. PNET and pancreatic adenocarcinoma are two distinct types of cancers, which have different clinical courses and molecular patterns and need different diagnostic procedures and treatment strategies. Survival of patients with PNETs seems to have increased over the last decades. The reason of better prognosis is not clear, improved imaging techniques and therapy may explain this phenomenon.[59]

5. Management

5.1 Surgical treatment

Surgical resection remains the only potentially curative treatment of PC. Unforunately less than 20% of the patients are eligable for an upfront resection at diagnosis. The main purpose of surgery is to achieve R0 resection, as only this can cure PC. Resectability is evaluated according to the consensus criteria based mainly on the degree of contact between the tumor and the vascular structures. Due to the high probability of R1 resection in borderline resectable disease, these patients are considered as candidates of the neoadjuvant approach in order to improve resection rates and outcome. Patients presenting with locally advanced pancreatic cancer or distant metastases have an unresectable disease stage and should receive palliative treatment.

The value of available imaging techniques is limited with regard to occult metastatic disease. Cancer located in the body or tail, large (>3cm) tumor size, highly elevated level of CA 19-9 increase the risk of small volume metastases. In these patients staging laparoscopy might be indicated before proceeding to surgery with curative intent.

The conventional surgical procedure for PC located in the head or uncinate process is a pancreatoduodenectomy or Whipple's procedure. It involves removal of the pancreatic head, gallbladder, distal portion of the common bile duct, duodenum, first 15 cm of the jejenum, lymph nodes and a partial gastrectomy. Three anastomoses are created for reconstrucion (pancreaticojejunostomy, choledochojejunostomy and gastrojejunostomy). Pylorus-preserving pancreaticoduodenectomy and subtotal stomach-preserving pancreaticoduodenectomy are important modifications in order to decrease the rate of postoperative complications (e.g., dumping, gastritis, delayed gastric emptying).[60]

For patients with a tumor in the body or tail of the pancreas a distal subtotal pancreatectomy combined with splenectomy can be recommended. Total pancreatectomy is a rarely applied procedure as it is frequently associated with diabetes. Pancreatic surgery should involve standard lymphadenectomy including the removal of more than 15 lymph nodes for accurate staging. Extended lymphadenectomy is not indicated.[61]

Vascular resection and reconstruction is a higly controversial issue regarding pancreatoduodenectomy. According to available data venous resection is a safe and feasible procedure, which should be considered in case of major vein (PV or SMV) involvement if R0 resection is achievable.[62] In contrast, arterial resection significantly increases mortility and morbidity and can be recommended only in selected patients.[63]

Basically, surgery for PC should be performed in high-volume centers only, in order to improve morbidity and mortality.

5.2 Oncological treatment

5.2.1. Radiotherapy

The GITSG randomised trial evaluated the role of adjuvant radiotherapy in PC. A substantial median survival benefit with 5-FU chemoradiation has been shown (21 months) in comparison to no adjuvant therapy (10.9 months).[64] After the results of this first study chemoradiotherapy became a standard treatment option in the adjuvant setting for resected pancreatic cancer in the United States.

In contrast, further randomised trials conducted in Europe have produced conflicting data. The EORTC study showed no significant survival benefit in favour of radiotherapy, moreover in ESPAC-1 even a deleterious effect of adjuvant chemoradiation has been suggested.[65,66] No benefit was observed even after R1 resection.

In addition to these results, a number of large retrospective analyses have been published showing conflicting results. In summary, due to the lack of evidence in large phase Ⅲ trials adjuvant radiotherapy or chemoradiotherapy should not be recommended as standard treatment.

Approximately 30-40% of PC patients have locally advanced or borderline resectable disease at diagnosis. There is no consensus about the optimal management of these patients. Patients with borderline resectable disease are more likely to have incomplete (R1) resection compared to primary resectable cases. Therefore, this population of patients is considered as the potential candidate of the neoadjuvant treatment approach including chemotherapy, radiotherapy or both. The main purpose of neoadjuvant therapy is to reduce tumor size, enhance R0 resection rates and finally survival. However, due to the lack of convincing evidence no clear statement regarding the best preoperative strategy can be given at the moment.

Initial chemoradiotherapy did not improve survival compared to chemotherapy alone.[67] Additionally, early developement of metastases has been seen in one third of the patients with non-resectable, non-metastatic disease. These patients are unlikely to benefit from locoregional treatment, therefore the use of unnecessary radiotherapy should be avoided. For the above reasons induction chemotherapy, followed by chemoradiation (with concurrent capecitabine) for non-progressing patients has been proposed as probably the most effective treatment strategy in this setting. However, survival benefit of the above approach is still lacking, patients should be treated in clinical trials if available. The same is true regarding the use of stereotactic body radiotherapy, an alternative to chemoradiotherapy. More studies are needed to demonstrate the role of radiotherapy in rendering non-resectable disease to resectable, and also to confirm survival benefit of this treatment modality. In contrast, for patients whose pain can not be adequately controlled using analgesics, radiotherapy should be considered as palliation strategy.

5.2.2. Chemotherapy

Adjuvant chemotherapy

Several randomized trials evaluated the role of postoperative chemotherapy in PC. In the landmark ESPAC-1 study patients receiving adjuvant 5-FU and folinic acid after

pancreatic resection had a significantly improved median survival (21.6 months vs 16.9 months) and estimated five-year survival (29% vs 11%) compared to no chemotherapy administered.[66] The CONKO-001 trial recruited patients between 1998 and 2004. The study confirmed the superiortity of 6 cycles gemcitabine compared to observation alone in terms of median disease-free survival (13.4 months vs 6.9 months) and median overall survival (22.8 months vs 20.2 months).[68] Finally, the largest adjuvant trial, ESPAC-3 compared 5-FU and folinic acid with gemcitabine after surgical resection. There was no significant difference in PFS and OS between the treatment arms. However, in patients with node positive disease or R1 resection the use of gemcitabine was associated with better outcome and less toxicity.[69] According to these results gemcitabine became gold standard for adjuvant therapy in routine clinical practice.

Two very recent trials are challenging the role of gemcitabine monotherapy. The JASPAC-01 study showed superiority of S1 (tegafur/gimeracil/oteracil) compared to gemcitabine in Japanese patients.[70] More data is needed to confirm these results in the West. Moreover, the results of the ESPAC-4 study support the use of gemcitabine plus capecitabine as standard of care after pancreatic resection.[71]

Neoadjuvant chemotherapy

As mentioned before, the use of induction chemotherapy, followed by chemoradiation has been suggested as the best choice of initial therapy in case of potentially resectable disease. However, the value of neoadjuvant treatment in LAPC patients with regard to render primary non-resectable cancer to resectable is highly controversial.

The optimal type of neoadjuvant chemotherapy is also a question of debate. Newer chemotherapy regimens such as FOLFIRINOX and nab-paclitaxel plus gemcitabin have shown efficacy in metastatic disease, but in the neoadjuvant setting there is no convincing evidence available for routine clinical practice.

Palliative chemotherapy

Until the introduction of gemcitabine, 5-FU was the only available agent in advanced PC. In 1997, gemcitabine became the the gold standard treatment option due to a significant survival benefit and fewer side effects compared to 5-FU. Gemcitabin also improved the clinical benefit response leading to reduction in pain intensity, daily analgesia consumption or improvement in Karnofsky performance status. Further trials evaluating the value of

gemcitabin monotherapy revealed a median survival of 5–7 months. Considering these results it is clear, that more effective systemic regimens are needed in order to improve outcome.

The FOLFIRINOX regimen has recently shown survival benefit compared to gemcitabine chemotherapy.[2] Previously untreated metastatic pancreatic cancer patients were randomized to receive either FOLFIRINOX or gemcitabine alone. Patients treated with the FOLFIRINOX regimen had a significantly improved median overall survival (OS) compared to the gemcitabine arm (11.1 months vs. 6.8 months). Additionally, improved progression free survival and higher response rate were seen in the experimental arm. Due to significant higher rate of grade 3 and 4 toxicities, the FOLFIRINOX regimen is considered as first line option for younger patients with good performance status in metastatic PC.

The multi-centre MPACT-trial compared the value of gemcitabine plus nab-paclitaxel combination therapy versus gemcitabine alone. Significant clinical benefits were seen in the experimental arm, achieving a median progression-free survival of 5.5 months and a median OS of 8.5 months.[3] Due to the favourable survival and toxicity data, gemcitabine + nab-paclitaxel became the first choice of systemic therapy for PC during the last years. However, in many countries nab-paclitaxel is still not reimbursed.

For second line therapy in metastatic PC nanoliposomal irinotecan in combination with fluorouracil and folinic acid has been recently shown to prolong survival with a manageable safety profile in patients who previously received gemcitabine-based therapy.[72]

5.3 Other treatment options

5.3.1. Endoscopic treatment

Endoscopic stent placement should be considered in case of biliary obstruction caused by tumors mostly located in the pancreatic head. If the tumor is unresectable metallic stents are preferred for biliary drainage, due to a longer patency period and fewer complications compared to plastic ones.

In contrast, preoperative biliary drainage in patients with potentially resectable PC is a question of debate. It seems reasonable to implement preoperative biliary decompression only in patients who present with symptoms of cholangitis or fever, severe pruritus or in whom operation is expected to be significantly delayed (more than 2 weeks).[73] It is also not clear whether plastic or metal stents should be used in this situation.

If gastrointestinal obstruction is present, endoscopic palliation using self-expendable enteral stents is a good alternative to enteral bypass surgery.

5.3.2. Invasive radiology

Radiofrequency ablation (RFA) and irreversible electroporation (IRE) are local ablative techniques representing a new innovation for the multimodality treatment of PC. The main indication of the above modalities is stage III PC. However, only results from small sudies are available on efficacy and safety, prospective, randomised data are still lacking.[74] The current existing evidence is not sufficient to propose these therapeutic options for routine practice.

6. Disease outcome

PC remains one of the most lethal type of malignancy worldwide. The overall five-year survival rate is about 6%, however, there is a wide variation among different countries.[75] For patients treated with upfront surgery and adjuvant therapy the median OS is approximately 11.2-25.5 months.[76] Despite the use of available oncotherapy overall survival for locally advanced disease is between 8.6–13.0 months, while the outcome of metastatic PC is even worse (mOS: 5.7-11.1 months).[2, 77]

7. Cancer registries

The main purpose of a cancer registry is the systematic collection, storage, analysis, interpretation and reporting of cancer patients data. Basically, there are two types of cancer registries, hospital-based and population-based registries.

The most relevant aspects of tumor data collection are as following: the incidence of cancer, environmental risk factors, the extent of disease at the time of diagnosis, the kinds and outcome of treatments applied. Cancer registries provide a valuable data source for researchers involved in the epidemiology, detection and management of cancer. The recognition of the causes of cancer may lead to introduction of preventive measures like screening programs. Earlier detection of cancer enhances the chance to find a more effective treatment. Long term follow-up data can help to evaluate the value of a certain kind of therapy. In some countries cancer registries incorporate also patient related outcome data, reflecting the growing importance of quality of life in cancer care.

Based upon the collected data, important public health decisions can be made in order to rationalize the utilization of limited resources. The costs of oncotherapy increased dramatically during the last 15 years. Beside the incredible cost of existing therapies, there are at least 100 new molecules for oncological purpose in phase III trials at the moment. For most health care systems it is almost impossible to finance all these treatments. Registries are becoming more and more valuable, as they can offer a very transparent and effective way to control the application of the approved drugs and provide information about the value of these therapies in the real world setting.

Considering all the above aspects, the Registry for Pancreatic Patients (RPP) was established in 2012. It is a web based data collection method. Data of 1600 patients from 34 Hungarian centers and 23 centres form abroad are currently in the system. More than 1000 blood samples were colleted for further research. The pancreatic cancer registry is a part of the RPP.

The original aim was to prospectively collect and analyse data of pancreatic cancer in the Hungarian population. Later on the decision was made to open the registry for other Eastern and Central European countries, which makes international data collection possible.

8. Multicenter prospective data collection and analysis by the Hungarian Pancreatic Study Group.

8.1 Patients and Methods

The Hungarian Pancreatic Study Group (HPSG) was established in 2012 in order to improve the care of patients suffering from pancreatic diseases. To achieve our aims we (i) developed an electronic data registry for patients (www.pancreas.hu) (ii) published the currently available evidence-based medicine (EBM) guidelines,[78, 79, 80, 81, 82] (iii) established specific study sessions including the pancreatic cancer one, (iv) and organized multicenter clinical trials.[83, 84, 85, 86]

For this study HPSG collected data from patients diagnosed with PC between September 2012 and March 2014 using uniform questionnaire and clinical data sheets. Patients were enrolled from 14 Hungarian centers including endoscopy units, gastroenterological, oncological and surgical departments. The characteristics of the single departments and the number of patients enrolled by each center are summarized in **Table 4.**

Name of institution	Type of institution	Department profile	Number of patients enrolled (n)
Borsod-Abaúj-Zemplén County General Hospital, Miskolc	General Hospital	Gastroenterology	2
Bács-Kiskun County Municipality Hospital, Kecskemét	General Hospital	Gastroenterology	2
Pándy Kálmán Békés County Hospital, Gyula	General Hospital	Gastroenterology	11
Department of Interventional Gastroenterology, National Institute of Oncology, Budapest	National Institution	Endoscopy Unit	27
Institute of Surgery, Clinical Center, University of Debrecen	University Hospital	Surgery	18
Department of Surgery, University of Pécs	University Hospital	Surgery	41
First Department of Medicine, University of Pécs, Hungary	University Hospital	Gastroenterology	29
First Department of Internal Medicine, University of Szeged	University Hospital	Gastroenterology	89
Second Department of Internal Medicine, University of Szeged	University Hospital	Gastroenterology	7
Department of Oncotherapy, University of Szeged	University Hospital	Oncology	18
Department of Surgery, University of Szeged	University Hospital	Surgery	55
First Department of Medicine, Szent György University Teaching Hospital of County Fejér, Székesfehérvár	General Hospital	Gastroenterology	43
First Department of Surgery, Semmelweis University, Budapest	University Hospital	Surgery	2
Dr. Rethy Pal Hospital, Békéscsaba	General Hospital	Gastroenterology	10

Table 4. Characteristics of the participating centers

Demographic data, data of possible risk factors, symptoms, diagnosis, staging, therapy and survival were assessed. Data collection was performed using a web-based electronic data collection method as part of The Registry for Pancreatic Patients (RPP).

Demographic data included age and gender of patients. Information about alcohol consumption and smoking (frequency and total amount of daily consumption), body mass index, history of acute and chronic pancreatitis, diabetes mellitus and familial pancreatic cancer has been collected as possible risk factors. Frequency of symptoms and clinical signs, such as fever, pain, diarrhea, jaundice and weight loss were also evaluated.

Cancer related data included the date of diagnosis, extension of the disease, localisation of the primary tumor, histological type, the method used to obtain histological diagnosis and the level of CA 19-9 at the time of diagnosis. Diagnosis and staging of pancreatic cancer was based on imaging tests including multi-detector computed tomography, magnetic resonance imaging, endoscopic retrograde cholangio-pancreatography and endoscopic ultrasonography. Primary resectable tumor, locally advanced and metastatic disease have been distinguished. Histological diagnosis was performed using brush cytology during ERCP, fine needle aspiration biopsy or surgical biopsy/resection.

The database included information on endoscopic, surgical, oncological and supportive therapy performed. The proportion of plastic or metal stents used for biliary drainage was determined. Information on the frequency of duodenal stent implantation was also recorded. Data on surgical resection (including margin status; R0, R1, R2) has been collected for patients with a resectable primary tumor. Palliative biliary and enteral bypass were recorded as well. If a patient received oncological treatment (radiation therapy or chemotherapy) for PC, the type and intent (neo-adjuvant, adjuvant, palliative) of therapy and the name of the chemotherapeutic agent used were also noted. Data collected on supportive therapy consisted of pancreatic enzyme replacement, pain control and the management of diabetes mellitus.

Information on survival status was obtained from the Hungarian Central Statistical Office. Survival was defined as the number of months between date of diagnosis and date of death (if known).

The research involved human participants. All data have been collected after patients had given written informed consent. The research had been approved by the Secretary of Medical Research Council, Scientific and Research Ethics Committee (Egészségügyi Tudományos Tanács Tudományos és Kutatásetikai Bizottság). The ethical approval number is 22254-1/2012/EKU (391/PI/2012.)

Statistical analysis

Statistical analysis with one-way ANOVA and student t-test was performed. Survival data were analysed by plotting Kaplan-Meier curves and LogRank test. A multivariate Cox-regression analysis was performed to identify independent predictors of overall survival. Variables with a p value of <0.2 were included in the Cox-regression analysis, in addition

gender and localisation of the tumor were added as arbitrary variables. Values are expressed as means ± standard deviation (SD) if not stated otherwise. A *P* value <0.05 was considered statistically significant.

8.2 Results

Three hundred fifty-four patients were enrolled into the study. Mean age of the population was 65.2 years (SD 11.5, range: 23 - 88 years). There were more males than females (53.4% vs. 46.6%, respectively).

Risk factors

One hundred and one patients (28.5%) have been recorded to smoke regularly. Twenty-eight patients (7.9%) were smoking more than 20 cigarettes per day. Alcohol consumption was reported in 97 patients (27.4%), whereas 44 (12.4%) were drinking alcohol on a daily basis. Data on Body Mass Index (BMI) at the time of diagnosis was available for 297 patients (83.9%). The time of diagnosis was defined as the date of the first imaging modality (CT scan, MRI or ERCP) performed giving the diagnosis of pancreatic cancer. One hundred seventy-one (57.6%) patients had a normal BMI (normal range: 18.5-24.99 kg/m^2), while 103 (34.6%) had overweight (BMI: 25.0-29.99 kg/m^2) and 23 (7.7%) were obese (BMI $\geq$ 30.0 kg/m^2). None of the patients was found to be underweight.

Only 8 patients (2.3%) had a positive history for recurrent acute pancreatitis, 13 (3.7%) were diagnosed with chronic pancreatitis. Approximately one third of the population (n=119, 33.7%) had diabetes; almost half (n=57, 47.9%) of them were using insulin. Positive family history for pancreatic cancer was found in 13 patients (3.6%).

Symptoms and signs

The most frequent symptoms at the time of diagnosis were abdominal pain and weight loss, (unexplained loss of more than 5% of the body weight within six month) which were present in 63.8% and 63% of all patients. Jaundice (bilirubin concentration higher than 35 μmol/L) was found in 52.5%. Interestingly, there was only a small difference in the frequency of jaundice between patients having a tumor in the pancreatic head (53.1%) and those having the cancer in the body or tail (50%). Diarrhea was recorded in 13.8% of the patients, 7.9% had fever. Newly diagnosed diabetes was found in 2.3% of the studied population. The cancer was recognized accidentally in 6.5%, these patients were symptom free. Presenting symptoms are summarized in **Figure 1.**

12. Figures

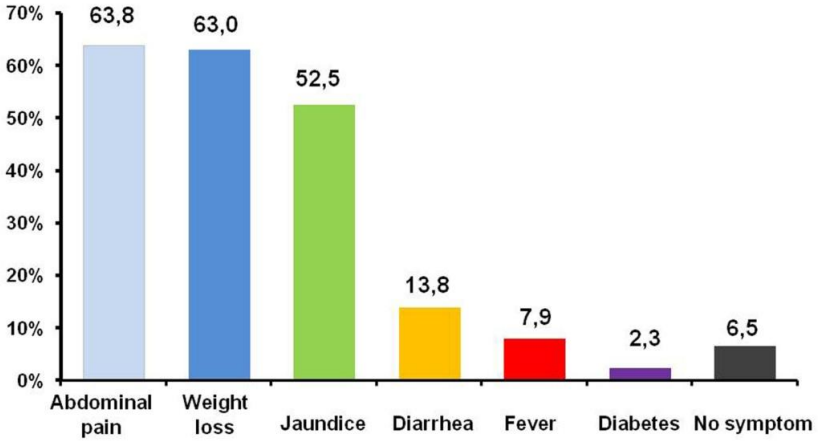

Figure 1. Incidence of symptoms and clinical signs at the time of diagnosis

Cancer related data

Information on tumor stage was missing in 29 cases (8.2%). Seventy-nine patients (24.3%) had resectable disease.

In the majority of cases (n=285, 80.5%) the primary tumor was located in the head of the pancreas. Cancer of the body and tail was found in 27 and 29 cases (7.6% and 8.2%, respectively). Tumor localization was unknown in 13 cases (3.7%).

The tumor was localized to the pancreatic head in the majority (77.2%) of resectable cases (n=61), while 7 (8.9%) patients had cancer located in the body and 11 (13.9%) in the tail of the pancreas. Hundred and thirty-eight cases (42.4%) were considered to be locally unresectable. One hundred and eight patients (33.2%) had metastatic cancer at initial diagnosis (**Table 5.**).

Disease stage	Number of patients (n)	Percentage (%)
Resectable	79	24.3
Locally advanced	138	42.4
Metastatic	108	33.2

Table 5. Distribution of pancreatic cancer cases by disease stage

Histological/cytological diagnosis was available for 227 patients (64.1%). The diagnosis was obtained via image guided fine needle aspiration biopsy (59.7%), brush cytology during ERCP (11.6%), or surgical biopsy/resection (28.7%). The biopsy revealed ductal adenocarcinoma in the majority of the cases (n=206, 90.7%). Adenocarcinoma of the papilla of Vater was confirmed in 5 cases (2.2%), while 12 patients (5.3%) had neuroendocrine carcinoma. There were 2 cases of intraductal papillary-mucinous carcinoma, one case with solid-pseudo-papillary carcinoma and one unique case with histologically proven diffuse large B-cell lymphoma located in the pancreas (**Figure 2**).

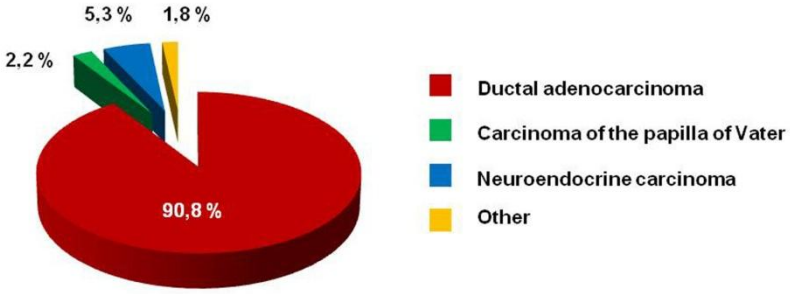

Figure 2. Distribution of pancreatic cancer cases by histological type

Serum CA 19-9 level was investigated for ductal adenocarcinoma and Vater's papilla carcinoma (n=211) at the time of initial diagnosis. Data were available for 83 patients. The level of CA 19-9 was elevated in 65 cases (78%), eighteen patients (22%) had normal values.

Therapy

Biliary stent implantation during ERCP was performed in 166 cases. Metal stents were used more common than plastic ones (59% vs. 40.1%, respectively). Duodenal stent placement for small bowel obstruction was reported in only two cases.

From the 79 patients with a resectable primary tumor, 60 underwent surgical resection. The distribution of tumor localisation of surgical cases was consistent with data reported on resectable cases: head: 50 (83.3%), body: 4 (6.7%), tail: 6 (10%). Fifty patients had tumor free resection margin (R0), four patients had microscopic (R1) and six macroscopic

(R2) residual disease. There is no information available why 19 patients with resectable pancreatic tumor did not undergo surgery. Palliative surgical treatment was performed in 84 cases. Thirty-five patients underwent enteral bypass, while biliary bypass reconstruction was performed in 49 cases (**Table 6.**).

Disease Stage	Type of surgery	Number of patients (n)
Resectable (n=79)	**Curative:**	60
	R0 resection	50
	R1 resection	4
	R2 resection	6
Unresectable (n=246)	**Palliative:**	84
	enteral bypass	35
	biliary bypass	49

Table 6. Surgical treatment

There is very limited data available in terms of the oncological treatment used in the studied population. Most information on oncotherapy originated from oncology departments presenting their cases. Only one patient was reported to have received radiotherapy with palliative intent for neuroendocrine carcinoma. Administration of chemotherapy was recorded in 42 cases. Nine patients received adjuvant treatment; palliative therapy was used in 33 cases. Every patient received gemcitabine-based chemotherapy. Neither the FOLFIRINOX regimen, nor nab-paclitaxel was used in this cohort of patients. There is no reported case in which neo-adjuvant chemotherapy was given.

Information about the use of analgesics was available in 179 patients (50.6%). Regular intake of painkillers was found in 73 cases (40.8%). Minor analgesics were needed for 56 patients (31.3%), while forty-three patients (24%) were administered major analgesics for severe pain. It should be noted, that 58.9% (43/73) of the patients suffering from pain would have needed major analgesics.

Exocrine pancreatic insufficiency (EPI) affects the majority of patients with pancreatic cancer. Pancreatic enzyme replacement therapy is recommended to relieve EPI-related gastrointestinal symptoms. Data on enzyme replacement therapy is available for 311

patients. Only 52 patients (16.7%) received pancreatic enzyme substitution in this cohort. Supportive treatment of the studied population is summarized in **Table 7**.

Type of therapy **(number of data available)**	**Number of patients (n)**	**Percentage (%)**
Analgesics **(n=179)**	73	40.8
Minor	56	31.3
Major	43	24
Pancreatic enzyme replacement **(n=311)**	52	16.7

Table 7. . Supportive treatment (some patients received both minor and major analgesics)

Survival

Survival data was available for 194 patients. Survival was defined as the number of months between the date of diagnosis and date of death. Overall survival (OS) for the whole population was 8.7 months.

OS of patients with histologically proven ductal adenocarcinoma (n=133) was 9.97 ± 1.77 months. Neuroendocrine carcinoma patients had a better prognosis with an OS of 14.00 ± 5.21 months. However, survival data is available for only 4 patients with neuroendocrine tumor. There is no information available about the survival of patients with carcinoma of the papilla of Vater.

OS of ductal adenocarcinoma patients was significantly different according to smoking habits (pLogRank=0.049 **Figure 3/A**) and for patients who have received gemcitabine based chemotherapy (p=0.013 **Figure 3/B**) in a Kaplan-Meier analysis. Since the number of curative surgical resections was low and survival data were not available from most of the patients OS was not analysed according to the surgical resection status. There was no association between gender (p=0.93), tumor stage (p=0.102), localisation (p=0.463), alcohol consumption (p=0.624), diabetes (p=0.597), presence of lymph node metastasis (p=0.873) or BMI (p=0.273) and overall survival. In a multivariate Cox-regression model,

smoking status and presence of gemcitabine-based chemotherapy were identified as independent predictors for overall survival (**Table 8.**)

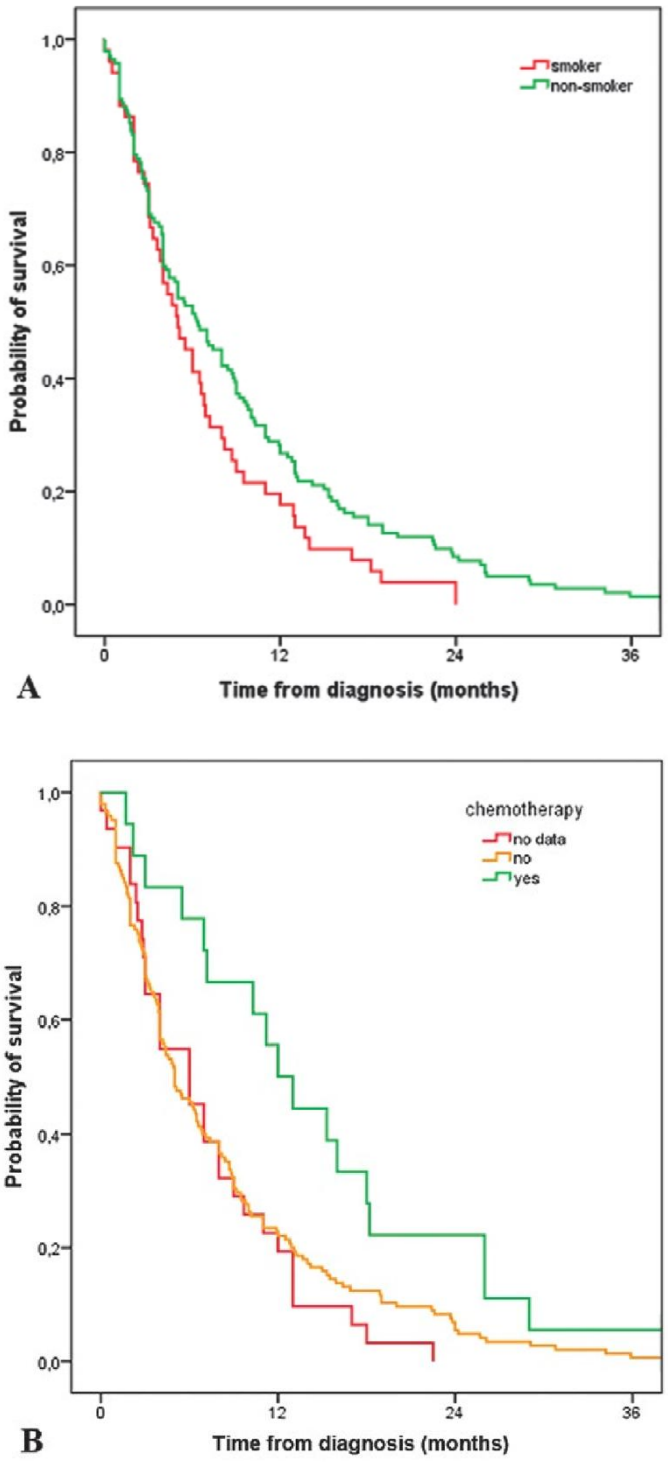

Figure 3. Overall survival of patients with pancreatic ductal adenocarcinoma according to smoking status **(A)** and presence of chemotherapy **(B)**

	P-value	**Hazard Ratio**	**95% CI**
gender	0.84		
alcohol consumption	0.15		
smoking	0.016		
Yes	0.016	1.61	1.10–2.37
No	Reference		
chemotherapy	0.045		
No data	0.016	2.08	1.15–3.77
No	0.027	1.75	1.07-2.88
Yes	Reference		

Table 8. Association between overall survival of patients with pancreatic ductal adenocarcinoma and gender, smoking status, alcohol consumption and chemotherapy

8.3 Discussion

Recently, pancreatic cancer has shown an increasing trend in incidence rates among both men and women.[87] The number of cases of PC in Central Europe is also increasing, mortality rates in this region are among the highest in the world.[7]

There is very limited data available about the management and outcome of pancreatic cancer in Hungary. In order to improve the prognosis of PC, it is essential to determine which factors contribute to the unfavorable mortality rates seen in Central Europe.

We report the first data from a large cohort of Hungarian pancreatic cancer patients. Patients were enrolled from departments with different profiles. Most of the data has been provided by university centres or general hospitals with teaching function. The proportion of patients enrolled by smaller hospitals was low, which is a limitation of the study. Data were compared to results from published literature.

There are multiple risk factors possibly related to PC. Smoking counts as the strongest environmental risk factor for PC. A meta-analysis reported an elevated risk of PC both for current and former smokers.[23] The rate of current smokers among patients with PC in the Hungarian cohort was the same (28.5%) as the average current smoker rate in the general

population (28.9% of the adult population were smoking in 2012 in Hungary). [88] These data do not support the relationship between smoking and the elevated risk of PC. Alcohol consumption contributes to episodes of acute pancreatitis, and is the most common cause of chronic pancreatitis. It seems reasonable that heavy alcohol consumption elevates the risk of PC. In the Hungarian cohort regular consumption of alcohol was reported in 27.4% of the patients. Data on diverse patterns of alcohol use in the general populaion are often inconsistent. However, the prevalence of heavy episodic drinking was 25.4% in the Hungarian population in 2010 (WHO).[89]

Chronic pancreatitis has been proposed as an independent risk factor for PC and explains about 3% of the cases.[90] In our study the prevalence of both acute recurrent and chronic pancreatitis was low. The rate of chronic pancreatitis was consistent with literature data. There were 13 patients with positive family history of pancreatic cancer; the youngest patient among them was 23 years old. Over the past decades multiple studies have reported a positive association between diabetes and PC.[29] However, as diabetes could be a manifestation of PC, the link between diabetes and the risk of cancer is controversial. New onset diabetes probably should be evaluated in a different manner than the diabetes lasting for more than 3 years. Hyperglycemia or manifest diabetes is present in 50-80% of patients diagnosed with PC. In this cohort, approximately one third of the patients had diabetes and half of them were using insulin at the time of diagnosis. There is no information about the duration of diabetes before the diagnosis of PC. New onset diabetes was found in only 2.3% of the studied population.

Obesity and overweight have been shown to be risk factors for PC.[91] Most of the patients in our study had a normal BMI or were overweight. The proportion of overweight and obese patients (34.6% and 7.7% respectively) in our cohort was comperable with data coming from the general population. Thirty-four percent of the Hungarian population were overweight and 18% were obese in 2007.[92]

Prevalence of the presenting symptoms was consistent with literature data. The most frequent symptoms at the time of diagnosis were abdominal pain and weight loss. The localisation of the tumor did not affect the prevalence of jaundice, which was present in more than a half of the patients. Histological diagnosis was not available in more than one third of the patients. In most cases histology was performed via image guided fine needle aspiration biopsy. In accordance with literature data,[93] histology revealed ductal adenocarcinoma in the

majority of the cases. Twelve patients had neuroendocrine carcinoma, while other subtypes were only found occasionally. In this study neuroendocrine carcinoma patients had a better prognosis than patients with ductal adenocarcinoma. Overall survival for the whole population was 8.7 months. The localisation of the tumor was predominantly in the head of the pancreas. Serum CA 19-9 level was found to be elevated in 78% of the cases with ductal adenocarcinoma and carcinoma of the papilla of Vater. The rate of false-negativity was 22%, which confirms that CA 19-9 determination can not be used as a screening test for the detection of pancreatic cancer.[94] About 15 to 20 percent of patients with PC have resectable disease at the time of diagnosis.[95] In this cohort more patients had resectable or locally advanced tumors (24.3% and 42.4%, respectively) as recorded in the literature. One third of the patients had metastatic disease at initial diagnosis. From the 79 patients with a resectable primary tumor 60 underwent surgical resection, most of them having R0 resection. Median survival following surgical resection ranges between 11.2 and 25.5 month.[76] Since OS data were available for only a few patients (n=9) who had undergone surgical resection, survival data were not analysed according to the surgical resection status. Information is lacking why 19 patients with resectable pancreatic tumor did not undergo surgery. Inappropriate overall status or comorbidities may have caused, that these patients were not eligible for surgery.

Biliary obstruction (defined as extrahepatic obstruction of the common bile duct causing jaundice [bilirubin>35 μmol/L]) was seen in 52.5% of the patients. It is controversial, whether metal or plastic stents should be used for biliary obstruction caused by PC. In a recent study the use of metal stents was associated with an outcome benefit.[96] In the Hungarian cohort metal stents were used more frequently than plastic ones. GI obstruction was resolved via palliative enteral bypass surgery in most of the cases. Endoscopic stent placement was performed in only two cases, which can be explained by the fact, that self-expandable enteral stents are not financially reimbursed therefore not available at the majority of Hungarian endoscopy units.

Information about oncological therapy was only available from oncology departments' patients. There was no recorded administration of radiotherapy for patients with ductal adenocarcinoma, which reflects that radiotherapy is not used in routine clinical practice for PC in Hungary. Gemcitabine-based chemotherapy was administered in all cases. Although, the FOLFIRINOX regimen has shown significant survival benefit for selected patients in PC,[2] there are only some centers in Hungary using this protocol, it is not used routinely. The nab-paclitaxel plus gemcitabine regimen has recently become a first-line

treatment option for patients with metastatic PC.[3] Nab-paclitaxel is currently not available in Hungary. There was no association between gender, tumor stage, localisation, alcohol consumption, diabetes, presence of lymph node metastasis or BMI and overall survival. Smoking status and presence of gemcitabine-based chemotherapy were identified as independent predictors for overall survival.

Information on supportive therapy is missing in many cases. It should be emphasized that the majority of patients suffering from pain would be in need for the use of major analgesics. Exocrine pancreatic insufficiency (EPI) affects the majority of patients with pancreatic cancer. Pancreatic enzyme replacement therapy is recommended to alleviate EPI-related gastrointestinal symptoms and improve quality of life. In the Hungarian cohort only 16.7% of the patients received pancreatic enzyme substitution.

8.4 Conclusions

The data collection and analysis performed by HPSG provides the first comparative dataset summarizing the situation of PC in Hungary. Data acquired so far are similar to data coming from western countries. Our results with regard to risk factors are comparable with existing literature data.

In the Hungarian cohort the frequency of both acute recurrent and chronic pancreatitis was low. Most patients had histologically proven ductal adenocarcinoma; the other histological subtypes were rare. The rate of resectability was similar to the results of population-based analyses performed in western countries. Palliative and supportive treatment strategies are increasingly becoming part of the routine daily practice. The proportion of patients with locally advanced disease versus metastatic cancer was larger than reported in the literature, however this had no effect on survival. Smoking status and presence of gemcitabine-based chemotherapy were identified as independent predictors for overall survival.

9. Our experience with Folfirinox therapy in locally advanced pancreatic cancer.

The aim of the present study was to prospectively collect and analyse data on efficacy and safety of FOLFIRINOX in LAPC patients. The secondary main objective was to assess the capability of FOLFIRINOX to render primary non-resectable cancer to resectable.

9.1 Patients and Methods

Consecutive patients diagnosed with locally advanced pancreatic cancer were enrolled into the study prospectively between january 2014 and november 2016. All patients had cytological or histological verification of pancreatic ductal adenocarcinoma. Only patients having locally advanced non-resectable disease were enrolled into the analysis, borderline resectable cases were excluded from the study. Tumor resectability was assessed through exploratory laparotomy or according to the radiologic definition criteria of resectability of the NCCN guidelines.[58]

Enrollment was limited to patients with good performance status (Eastern Cooperative Oncology Group performance status score of 0 or 1), adequate bone marrow parameters (Absolute Neutrophil Count, $\geq 1.5 \times 10^9$/L and platelet count, ≥100,000 G/L), liver function (bilirubin ≤1.5 times the upper limit of the normal range), and renal function.

A modified FOLFIRINOX protocol was used: no bolus fluorouracil was given and a 20% dose reduction of oxaliplatin and irinotecan was applied from the beginning of the therapy. The following regimen was applied: oxaliplatin, 70 mg per square meter of body-surface area; irinotecan, 145 mg per square meter; and leucovorin, 400 mg per square meter given as a bolus followed by 2400 mg fluorouracil per square meter given as a 46-hour continuous infusion, every 2 weeks.

Primary prophylaxis of chemotherapy-induced febrile neutropenia using granulocyte colony-stimulating factor (G-CSF) was applied. Subcutaneous injection of filgastrim 48 MU/0.5 ml was administered for 5 consecutive days starting 5 days after each cyle of FOLFIRINOX.

Treatment response was assessed every 2 months after beginnig of chemotherapy using multiple detector computed tomography. The level of CA 19-9 was determined at the same time as CT was performed. After finishing FOLFIRINOX treatment, further follow up measurements were performed every 3 months.

Statistical analysis

For categorical data frequency distributions were determined, for continuous variables medians and interquartile ranges were calculated. Chi-squared test was used to evaluate differences within subgroups of patients. For time-dependent survival outcomes Kaplan-

Meier analysis was performed. A p value of <0.05 was regarded as statistically significant. Statistical analysis was performed using SPSS software v. 20.0 (Chicago, IL).

Ethical statement

The study complies with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Research Ethics Committee.

9.2 Results

Patient characteristics

Data of thirty-two consecutive patients have been collected and analised. Median age of the population was 62 years (IQR: 51-67.8 years). There were more males than females (53.1% vs. 46.9%, respectively). All patients had ECOG performance status of 0 or 1. In the majority of the cases (59.3%) the tumor was localised in the head of the pancreas. Stent placement for biliary occlusion was performed in 8 cases (25%) before starting therapy. In 18 patients (56.2%) non-resectable disease was assessed through exploratory laparotomy. Patient characteristics are summarized in **Table 9.**

Number of patients	32
Age	mean: 60.2 years, min-max 40-77 y.
Gender (male/female)	17/15 (53.1/46.9%)
ECOG PS	ECOG 0: 21 (65.3%) ECOG 1: 11 (34.7%)
Localisation • head • body • tail • processus uncinatus	 19 (59.3%) 7 (21.8%) 4 (12.5%) 2 (6.3%)
Stent implantation	8 (25%)
Explorative laparotomy	18 (56.2%)

Table 9. Patient characteristics

Chemotherapy related data

Treatment plan included the administration of maximum 12 FOLFIRINOX cycles. The mean number of Cx cycles applied was 6.9 (range: 2-12). With the exception of one patient receiving previous gemcitabine, FOLFIRINOX was used as first line therapy in all cases. Further dose reduction was needed in approximately one third of the patients (34.3%),

while six patients (18.8%) discontinued treatment for toxicity. Second line chemotherapy was feasible in 74.2% of the cases treated with FOLFIRINOX as first line regimen. (**Table 10**). FOLFIRINOX reinduction was applied in one case, all other patients received gemcitabine-based therapy as second line treatment. Erlotinib was used in two cases as combination with gemcitabine, while nab-paclitaxel was administered in one patient. Currently nab-paclitaxel is not reimbursed in Hungary for the treatment of PC.

Number of Cx cycles	6.9
FOLFIRINOX as 1st/2nd line therapy	31/1 (97/3/%)
Dose reduction	11 (34.3%)
Dose discontinuation	6 (18.8%)
2nd line treatment	23/31 (74.2%)

Table 10. Chemotherapy related data

Treatment response

Treatment response was evaluated every 2 months, using CT scan and measurement of CA 19-9 level while patients were on treatment. Best response to therapy (range: 2-6 months after beginning of FOLFIRINOX) was stable disease (SD) in 18 cases (56.2 %), partial regression (PR) was seen in 6 cases (18.8%). Rapid disease pogression occured in 8 patents (25%). The rate of progressive disease was 53.3% at 6 month and 76.7% at 9 month after the beginning of FOLFIRINOX. Only 2 patients (6.3%) underwent surgical resection with curative intent. R0 resection could have been achieved in both cases (**Table 11**.).

Determination of CA 19-9

The level of serum CA 19-9 was followed up before the beginning of FOLFIRINOX therapy and while patients were on treatment. Elevated CA 19-9 was found in 24 (75%) of the cases at diagnosis. Normalisation or decrease of tumor marker values were seen in four out of six cases with objective tumor response (PR). No improvement of CA 19-9 level was detected in case of disease progression (**Table 12.**).

Best response	Treatment response 2 months	Treatment response 4 months	Treatment response 6 months	Treatment response 9 months
CR: 0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PR: 6 (18.8%)	5 (15.6%)	3 (9.7%)	3 (10%)	2 (6.7%)
SD: 18 (56.2%)	19 (59.4%)	16 (51.6%)	11 (36.7%)	5 (16.6%)
PD: 8 (25%)	8 (25%)	12 (38.7%)	16 (53.3%)	23 (76.7%)
Resection rate for locally advanced disease (**LAPC**): 2/32 (6.3%) **Resection rate** in case of **radiologic regression**: 2/6 (33.3%)				

Table 11. Treatment response and resection rate

CA 19-9 level at diagnosis (U/ml)	Best CA 19-9 level after start of FOLFIRINOX (U/ml)
499	104
>1200	106
>1200	>1200
341	78
932	28
32	12

Table 12. Change in the serum CA 19-9 levels of patients with partial regression (PR)

Toxicity

Nausea (62.5%) and fatigue (71.9%) were noted as the most frequent adverse events (with severity grades 3 or 4 of 18.8% and 12.5% respectively). Alopecia occured in 34.4% of the patients. Regarding hematologic toxicity neutropenia was observed in 43.8%, with a 28.1% rate of grade 3/4 events. As a result of the application of primary G-CSF prophylaxis there was only one documented case of febrile neutropenia. Another patient was hospitalized for a life-threatening septic condition leading to multiple organ failure caused by *Clostridium difficile* infection. Treatment was discontinued for toxicity in 6 patients (18.8%). Incidence rates of hematologic and non hematologic toxicity are summarized in **Table 13**.

Non hematologic toxicity:				
Toxicity	**Frequency**		**Gr. 3-4**	
nausea	62.5 %		18.8%	
fatigue	71.9%		12.5%	
vomiting	31.3%		18.8%	
neuropathy	28.1 %		0%	
diarrhea	46.9%		12.5%	
alopecia	34.4 %		NA	
Hematologic toxicity:				
neutropenia	**Gr. 3-4 neutropenia**	**febrile neutropenia**	**anemia**	**thrombopenia**
43.8 %	28.1%	3.1%	25%	15.6%

Table 13. Hematologic and non hematologic toxicity associated with FOLFIRINOX

Survival

PFS and overall survival were analysed. Median time to disease progression was 148 (IQR: 58-228) days in patients with disease progression. The probability of disease progression was 25% and 50% after 75 and 160 days with 88.4% of possibility of disease progression after 500 days. (**Figure 4.**)

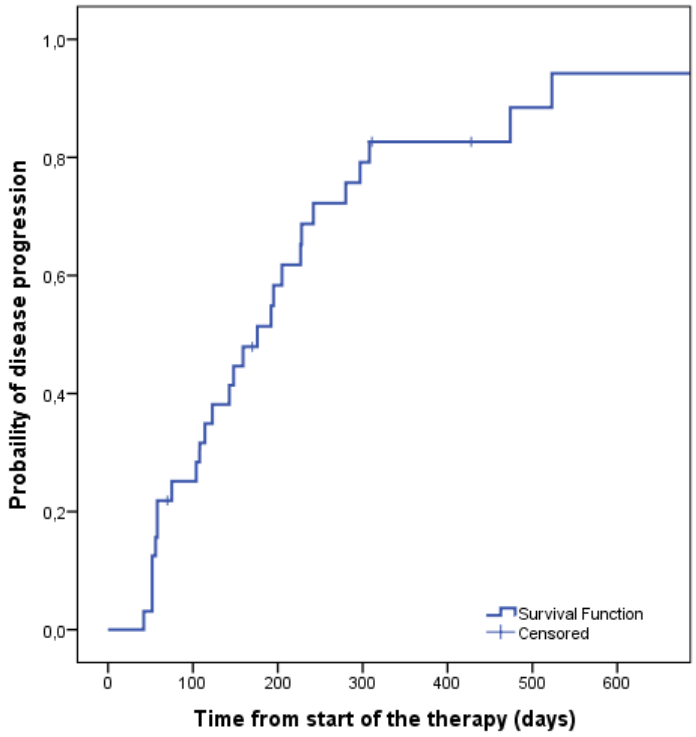

Figure 4. Probability of disease progression

OS probability was 92.1, 71.5% and 49.5% at 180-, 365 and 540 days. Median time to death was 312 (IQR: 225-450) days (**Figure 5.**).

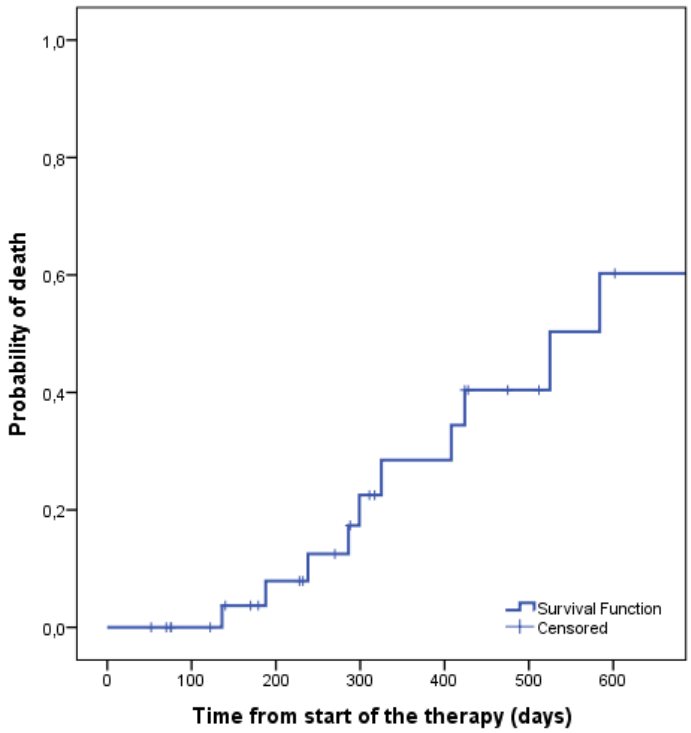

Figure 5. Probability of death

9.3 Discussion

The main finding of our present study was that FOLFIRINOX-based treatment regimen was associated with disease control in a high proportion of LAPC patients coupled with a survival benefit. However, the present data does not support the capability of FOLFIRINOX to render primary non-resectable cancer to resectable and it was associated with a high rate of adverse events.

The management of LAPC remains controversial. It is questionable whether neoadjuvant treatment is capable to render primary non-resectable disease to resectable. Treatment options include radiotherapy, chemoradiotherapy, and chemotherapy alone. The optimal strategy to perform neoadjuvant therapy is also unknown. Most of these patients are enrolled in clinical studies testing the diferent therapeutic regimes. Most studies evaluating the value of FOLFIRINOX in LAPC are coming from the US and Europe and have a small sample size and a retrospective design (**Table 14.**) Treatment results, such as objective

response rate (range 12-50%), median progression free survival (range: 10.3-17.8 months), median overall survival (range: 14.8-26.6 months) and the rate of resection (6-44%) varied greatly between studies. A recent meta-analysis suggests, that FOLFIRINOX is more effective compared to gemcitabine in this setting.[97]

References	Study design	n	CR %	PR %	SD %	PD (%)	ORR (%)	DCR (%)	Resection rate (%)	mPFS months	mOS months
Conroy[98]	phase II	11	NA	NA	NA	NA	27	na	na	na	na
Gunturu[99]	retrospective	16	6	44	44	0	50	94	**na**	**na**	**na**
Hosein[100]	retrospective	18	NA	NA	NA	NA	NA	NA	28	NA	NA
Faris[101]	retrospective	22	NA	NA	NA	NA	27.3	NA	22.7	11.7	NA
Peddi[102]	registry	18	6	28	50	17	34	84	**NA**	**NA**	**NA**
Marthey[109]	prospective database	77	NA	NA	NA	NA	28	84	36	NA	NA
Rombouts[103]	retrospective	18	NA	NA	NA	NA	12	NA	6	10.3	14.8
Blazer[104]	retrospective	26	NA	NA	NA	NA	NA	NA	44	0	0
Mahaseth[107]	retrospective	24	NA	NA	NA	NA	NA	NA	NA	13.7	17.8
Boone[105]	retrospective	13	NA	NA	NA	NA	NA	NA	10	NA	NA
Moorcraft[106]	retrospective	22	NA	NA	NA	NA	NA	NA	NA	12.9	18.4
Stein[108]	phase II	33	NA	NA	NA	NA	17.2	NA	41.9	17.8	26.6

Table 14. Efficacy of FOLFIRINOX in LAPC studies. (CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; mPFS, median progression free survival; mOS, median overall survival)

We included 32 consecutive patients receiving FOLFIRINOX for LAPC at our department. Borderline resectable cases were excluded. The patients belonged to a younger age group and were all fit for chemotherapy (ECOG PS: 0/1). In more than half (56.2%) of the patients explorative laparotomy was performed and confirmed non-resectable cancer.

Considering the fact, that FOLFIRINOX can lead to significantly increased toxicity, a number of modified regimens are in use by different institutions. Modification can affect the dose of oxaliplatin and irinotecan, or the administration of bolus 5-FU can be omitted. Many publications report decreased rate of adverse events beside maintained efficacy, however only data from small series are available.[107] Recently a prospective phase II study confirmed favourable safety and efficacy profile regarding modified FOLFIRINOX.[108] We applied a modified protocol; attenuated doses of oxaliplatin and irinotecan were given and no bolus 5-FU was used.

Folfirinox was used as first line therapy in the majority of patients (97%). Best response to therapy was SD or PR in 75% of the cases. The rate of progressive disease at 6 and 9 month after the beginning of FOLFIRINOX was 53.3% and 76.7% respectively.

Probability of PFS was 75%, 50% and 11.6% after 75, 160 and 500 days. Marthey et al reported the results of a multicenter cohort of 77 LAPC patients treated with FOLFIRINOX.[109] Within the cohort, 1-year PFS rate was 59% and 1-year OS rate was 77%. Of note, the probability of OS at 1-year in the present study was 71.5%.

Radiologic regression was detected in six (18.8%) patients however, surgical resection was feasible in only 2 cases. Both patients had previous explorative laparotomy revealing unresectability before starting FOLFIRINOX. After performing neoadjuvant treatment (8 and 12 cycles) R0 resection could have been achieved in both cases, in one case histology revealed a good pathologic regression with only a small residual tumor remaining. The rate of resection was 6.3%, which stays below the results reported in the literature. A systematic review evaluated the results of 292 patients with LAPC treated solely with FOLFIRINOX, the resection rate was 12% (70% R0), with 15.7 months median OS.[110]

The use of the CA19-9 tumor marker has been widely accepted in the management of PC. Clinical usefulness of CA 19-9 was reported in early diagnosis, assessment of resectability and monitoring progression of PC.[46] The level of CA 19-9 was elevated in 75% of our patients. The change in the value of the tumor marker correlated well with treatment response in our study.

Despite dose reduction of oxaliplatin and irinotecan significant rate of toxicity was detected. The most frequent grade 3/4 adverse events were nausea, fatigue and diarrhea, incidence rates were comperable with the results of the randomised trial conducted by Conroy et al.[2] Grade 2 alopecia occured in 34.4% of the patients which is more than reported previously. Due to the application of primary G-CSF prophylaxis, the incidence of grade 3/4 neutropenia was lower (28.1%) with only one documented case of febrile neutropenia. One patient was successfully treated for septic *Clostridium difficile* infection associated with the use of FOLFIRINOX. Treatment had to be discontinued for toxicity in 18.8% of the patients.

In metastatic PC nanoliposomal irinotecan in combination with fluorouracil and folinic acid has been recently shown to prolong survival with a manageable safety profile in patients who previously received gemcitabine-based therapy.[72] Due to the favourable survival and toxicity data, the use of gemcitabine +/- nab-paclitaxel, followed by second line treatment with nanoliposomal irinotecan sholuld be considered as treatment possibility also for locally

advanced disease not eligable for surgical resection. Further investigations are needed to confirm the results also in the non-metastatic setting.

9.4 Conclusions

According to the high disease control rate and survival data found in our study, FOLFIRINOX might be an effective choice for first line therapy for LAPC patients. However, our data does not support the capability of FOLFIRINOX to render primary non-resectable cancer to resectable. Different patient selection, further modifications of the original regimen, or combination with radiotherapy might improve resection rates and survival. Despite reduced chemotherapy doses, significant toxicity has been observed. Frequency of adverse events may prevent long term ulitization of FOLFIRINOX therapy. The use of primary G-CSF prophylaxis was effective to prevent febrile neutropenia. The clinical value of CA 19-9 determination was confirmed in our study. In conclusion, further investigations are needed to determine the role of FOLFIRINOX in LAPC.

10. Conclusions and future perspectives

PC is one of the most lethal human malignancies; the number of patients with PC is increasing globally. Data suggest that the onco-epidemiological situation related to pancreatic cancer in Central European countries is even worse compared to that in the Western world. There is only limited information available on the management of PC from Central Europe including Hungary.

The recognition of the causes of cancer may lead to introduction of preventive measures like screening programs. Earlier detection of cancer enhances the chance to find a more effective treatment. In order to improve outcome of PC, it is essential to determine which factors contribute to the unfavorable trends seen in less developed countries. Cancer registries provide a valuable data source for researchers and clinicians and can be extremely helpful to make the management of PC more effective.

The Hungarian Pancreatic Study Group (HPSG) conducted a multicenter prospective study in order to collect and analyse demographic data, data of possible risk factors, symptoms, diagnosis, staging, therapy and survival associated with PC. To our knowledge these are the first reported results of a PC cohort in Hungary, which underlines the importance of the collected data. Data acquired so far are similar to data coming from western countries. Our results with regard to risk factors are comparable with existing literature data. In the

Hungarian cohort the frequency of both acute recurrent and chronic pancreatitis was low. Most patients had histologically proven ductal adenocarcinoma; the other histological subtypes were rare. The rate of resectability was similar to the results of population-based analyses performed in western countries. Palliative and supportive treatment strategies are increasingly becoming part of the routine daily practice. The proportion of patients with locally advanced disease versus metastatic cancer was larger than reported in the literature, however this had no effect on survival. The main finding of our study was that smoking status and presence of gemcitabine-based chemotherapy were identified as independent predictors for overall survival.

Future plans of the Hungarian Pancreatic Study Group include improving the quality of data collection and the extension of the database to other Central and Eastern European countries.

The management of PC remains a big challenge. Surgery with or without the use of preoperative therapy is the only curative treatment option. However, the optimal strategy for the neoadjuvant approach is still lacking. In a single center study we assessed the efficacy and safety of FOLFIRINOX chemotherapy in LAPC patients. According to the high disease control rate and survival data found in our study, FOLFIRINOX might be an effective choice for first line therapy in LAPC patients. However, our data does not support the capability of FOLFIRINOX to render primary non-resectable cancer to resectable.

Further investigations are needed to identify the most effective treatment in order to improve outcome in PC. Cancer registries are becoming more and more valuable, as they incorporate data on the causes, diagnosis, extent, therapy and outcome of a type of different malignancies. Besides, registries can offer a very transparent and effective way to control the application of new treatment options and provide information about the value of these therapies in the real world setting. As the costs of oncotherapy have increased dramatically during the last two decades, the rationalisation of our resources available for cancer care is essential.

During the past few years, new chemotherapy regimens became available for patients with pancreatic adenocarcinoma. However, median survival rates improved only marginally, the management of PC is still not resolved. Unlike to other tumor types, the results of molecular targeted therapies are disappointing for PC. In contrast, cancer immunotherapy resulted in survival benefit for lung, kidney, bladder and other tumor types recently and

immune mediators are being tested also in PC. Currently, immuntherapy counts as the most promising approach how to treat pancreatic cancer in the near future.

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