COMPLEX CLINICAL EVALUATION OF PANCREATIC CANCER
THE ROLE OF REGISTRIES IN DATA ANALYSIS OF MALIGNANT DISEASES

Ph.D. Thesis

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INTRODUCTION

Pancreatic cancer (PC) is one of the most aggressive types of human malignancies and to present it remains a major health problem. The number of cases with PC is increasing worldwide. In 2012, there were 103,773 newly diagnosed cases and 104,463 fatal outcomes in Europe. 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. There are data reporting even higher incidence and mortality rates in Central Europe compared to western countries. The rate of PC in 2012 was highest in the Czech Republic, followed by Slovakia, Armenia and Hungary. The number of new cases was 2,373, while 1,837 died due to PC in Hungary in 2010.

Pancreatic cancer is known to affect older individuals, less than 10% of patients with PC are below the age of 50. There are differences by sex and race in the incidence and mortality of the disease.

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. For patients treated with upfront surgery and adjuvant therapy the median overall survival (mOS) is approximately 11.2-25.5 months. 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).

The exact causes of pancreatic cancer are not known. Family history is present in approximately 5 to 10 percent of PC patients. Genetic susceptibility loci such as BRCA2, PALB2, CDKN2a and ATM have been intensively studied in relation to the risk of PC. Patients with certain hereditary syndromes are considered to have high risk of developing PC.

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, while dietary factors seem to be less important. The role of chronic pancreatitis, alcohol abuse, overweight and diabetes mellitus is still controversial.

Symptoms and signs are non-specific for PC and appear often in advanced stage. Clinical usefulness of CA 19-9 was reported in early diagnosis, assessment of
response to chemotherapy and monitoring progression of PC. However, there are no screening tests for early detection of PC currently.

Transabdominal ultrasound (US) is one of the first tests for a patient presenting with gastrointestinal symptoms. Abdominal computer tomography (CT) counts as the "gold standard" imaging modality for PC. Since its introduction in the early 1990s endoscopic ultrasound (EUS) has become an essential tool for diagnosis and staging of pancreatobiliary disorders.

Histologic confirmation is needed before starting oncotherapy for PC. The biopsy can be performed using percutaneous fine-needle aspiration (FNA) with either US or CT guidance, or more recently EUS-guided FNA. Fit patients with potentially resectable disease do not necessarily need a biopsy before surgery. The most preferred staging system for PC is the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM classification.

Surgical resection remains the only potentially curative treatment of PC. Unfortunately less than 20% of the patients are eligible for an upfront resection at diagnosis. The conventional surgical procedure for PC located in the head or uncinate process is a pancreatoduodenectomy or Whipple’s procedure. For patients with a tumor in the body or tail of the pancreas a distal subtotal pancreatectomy combined with splenectomy can be recommended. Radical surgery is a highly controversial issue regarding PC. According to available data venous resection is a safe and feasible procedure, which should be considered in case of major venous (PV or SMV) involvement if R0 resection is achievable. In contrast, arterial resection significantly increases mortality and morbidity and can be recommended only in selected cases. Basically, surgery for PC should be performed in high-volume centers only, in order to improve morbidity and mortality.

The main purpose of surgery is to achieve R0 resection, as only this can cure PC. 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. The optimal type of neoadjuvant chemotherapy is also a question of debate. Patients should be treated in clinical trials if available. In routine clinical practice the use of induction chemotherapy, followed by chemoradiation has been suggested as the best choice of neoadjuvant treatment.
The use of adjuvant gemcitabine-containing chemotherapy is indicated after surgical resection of PC in order to reduce the risk of recurrence and improve survival. The newest results support the use of gemcitabine plus capecitabine as standard of care after pancreatic resection. Currently, adjuvant radiotherapy or chemoradiotherapy should not be recommended as standard treatment.

Palliative chemotherapy can be recommended for patients with locally advanced or metastatic disease. The FOLFIRINOX regimen has recently shown survival benefit compared to gemcitabine chemotherapy, the regimen is considered as first line option for younger patients with good performance status in metastatic PC. Nab-paclitaxel in combination with gemcitabine has also been approved as first-line treatment option for metastatic PC. For second line therapy nanoliposomal irinotecan in combination with fluorouracil and folinic acid has been recently shown to prolong survival in patients who previously received gemcitabine-based therapy. However, the new agents are not reimbursed in Hungary at the moment.

Cancer registries are about to become more and more important in the future. Registries provide a valuable data source for researchers involved in the epidemiology, detection and management of cancer. 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. Registries 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.

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. In order to improve outcome of PC, it is essential to determine which factors contribute to the unfavorable trends seen in less developed countries.

Considering all the above aspects, the Registry for Pancreatic Patients (RPP) was established by the Hungarian Pancreatic Study Group (HPSG) in 2012. 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.
**AIMS**

1. Multicenter prospective data collection and analysis on pancreatic cancer

   The aim of the study was to prospectively collect and analyse data of pancreatic cancer in the Hungarian population. Demographic data, data of possible risk factors, symptoms, diagnosis, staging, therapy and survival were assessed. The association between survival and possibly related factors has been investigated.

2. Our experience with FOLFIRINOX therapy in locally advanced pancreatic cancer

   Our purpose 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.

**PATIENTS AND METHODS**

1. Multicenter prospective data collection and analysis on pancreatic cancer

   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.

   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, 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 evaluated as well.
Cancer related data included the date of diagnosis, extension of the disease, location 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.

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).

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 location 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.
2. **Our experience with FOLFIRINOX therapy in locally advanced pancreatic cancer**

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.

Enrollment was limited to patients with good performance status (Eastern Cooperative Oncology Group performance status score of 0 or 1), adequate bone marrow parameters, liver and renal function.

In order to reduce toxicity 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.

Treatment response was assessed every 2 months after beginning 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.

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

**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-
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).

RESULTS

1. Multicenter prospective data collection and analysis on pancreatic cancer

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). There are multiple factors possibly related to PC, smoking counts as the strongest environmental risk factor. 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). Heavy alcohol consumption elevates the risk of PC. In the Hungarian cohort regular consumption of alcohol was reported in 27.4% of the patients, whereas 12.4% were drinking alcohol on a daily basis. Obesity and overweight have also been shown to be risk factors for PC. In our study 34.6% of the patients had overweight and 7.7% were obese.

In our study the prevalence of both acute recurrent and chronic pancreatitis was low, which is consistent with literature data. Approximately one third of the population (33.7%) had diabetes; almost half (47.9%) of them were using insulin. New onset diabetes was found in only 2.3% of the studied population. There were 13 (3.6%) patients with positive family history of pancreatic cancer.

Prevalence of the presenting symptoms was consistent with literature data. The most frequent symptoms at the time of diagnosis were abdominal pain (63.8%) and weight loss (63%). The location of the tumor did not affect the prevalence of jaundice, which was present in more than half (52.5%) of the patients. The cancer was recognized accidentally in 6.5%, these patients were symptom free.

In the majority of cases (80.5%) the primary tumor was located in the head of the pancreas. Cancer of the body and tail was found in 7.6% and 8.2%, respectively. Histology revealed ductal adenocarcinoma in the majority of the cases (90.7%), while 12 patients (5.3%) had neuroendocrine carcinoma. 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%). Serum CA 19-
9 level was found to be elevated in 78% of the cases with adenocarcinoma, while it was normal in 22% of the patients.

Seventy-nine patients (24.3%) had resectable disease at initial diagnosis, while 138 (42.4%) were considered to have locally unresectable and 108 (33.2%) metastatic cancer. From the 79 patients with a resectable primary tumor, 60 underwent surgical resection, the rate of R0 resection was 83.3%. Palliative surgical treatment was performed in 84 cases. Thirty-five patients underwent enteral bypass, while biliary bypass reconstruction was performed in 49 cases. Biliary stent implantation during ERCP was performed in 166 cases. Metal stents were used more common than plastic ones (59% vs. 41%, respectively). Duodenal stent placement for small bowel obstruction was reported in only two cases.

There is limited data available in terms of the oncological treatment used in the studied population. Administration of chemotherapy was recorded in 42 cases. Gemcitabine-based chemotherapy was used in all cases. There was no recorded administration of FOLFIRINOX or nab-paclitaxel, which reflects that these therapies are not used routinely in Hungary. The same can be said about the application of radiotherapy for PC.

Regular intake of painkillers was found in 40.8% of the cases. It should be noted, that 58.9% of the patients suffering from pain would have needed major analgesics. Only 16.7% of the patients received pancreatic enzyme substitution in this cohort.

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.

OS of ductal adenocarcinoma patients was significantly different according to smoking habits (pLogRank=0.049) and for patients who have received gemcitabine based chemotherapy (p=0.013) in a Kaplan-Meier analysis (Figure 1.). 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, tumor stage, location, alcohol consumption, diabetes, presence of lymph node metastasis or BMI and overall survival.
Figure 1. Overall survival of patients with pancreatic ductal adenocarcinoma according to smoking status (A) and presence of chemotherapy (B)

2. Our experience with FOLFIRINOX therapy in locally advanced pancreatic cancer

Data of thirty-two consecutive patients have been collected and analyzed. 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). The mean number of Cx cycles applied was 6.9. With the exception of one patient receiving previous gemcitabine, FOLFIRINOX was used as first line therapy in all cases.

Best response to therapy was stable disease (SD) in 56.2% of the cases, partial regression (PR) was seen in 6 cases (18.8%).

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 2.).
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 3.).
Surgical resection was feasible in only 2 patients (6.3%). R0 resection could have been achieved in both cases.

The level of CA 19-9 was elevated in 75% of our patients. 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.

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 occurred 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.

**CONCLUSIONS**

1. **Multicenter prospective data collection and analysis on pancreatic cancer**

   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 regarding risk factors are comparable with existing literature data.

   In the Hungarian cohort the frequency of both acute recurrent and chronic pancreatitis was low. Approximately one third of the population had diabetes. 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.
2. **Our experience with FOLFIRINOX therapy in locally advanced pancreatic cancer.**

   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 utilization of FOLFIRINOX therapy. The clinical value of CA 19-9 determination was confirmed in our study.

**LIST OF PUBLICATIONS**

**PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS**


**PUBLICATIONS NOT RELATED TO THE SUBJECT OF THE THESIS**


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