**lek. Marta Fudalej**

**Ocena prognostycznej wartości wybranych czynników klinicznych i patomorfologicznych w grupie pacjentów**

**z rozpoznaniem raka trzustki**

**Rozprawa na stopień doktora nauk medycznych** **i nauk o zdrowiu**

**w dyscyplinie nauki medyczne**

Promotor: prof. dr hab. n. med. i n. o zdr. Anna Badowska-Kozakiewicz

Zakład Propedeutyki Onkologicznej

Warszawskiego Uniwersytetu Medycznego



Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych

Warszawskiego Uniwersytetu Medycznego

Warszawa 2024 r.

**Streszczenie w języku angielskim**

**Title**

Assessment of the prognostic value of chosen clinical and pathomorphological factors in the group of patients with diagnosed pancreatic cancer.

**Introduction**

Pancreatic cancer (PC) is the sixth leading cause of cancer-associated deaths in Poland, according to statistical reports gathered in 2021. The five-year overall survival (OS) rate is less than 10%. Poor prognosis is associated with several factors, encompassing a long asymptomatic course of disease and frequently observed resistance to most conventional treatment options. Complete surgical resection provides the only chance for a cure; however, only 20% of patients are diagnosed with resectable disease.

Comorbidities are one of the most meaningful clinical aspects of patients with PC. The patient's general condition and comorbidities influence the choice of oncological treatment, further treatment response, and survival.

**The aims of the doctoral dissertation**

The main objective of the doctoral dissertation was to identify variables associated with comorbidities that influence the prognosis of patients with PC.

Specific objectives:

1. Identifying variables influencing the prognosis of patients with PC and diabetes mellitus (DM). Analysing DM's impact on the course of treatment and prognosis.
2. Identifying variables influencing the prognosis of patients with PC and hypertension (HTN). Analysing HTN influence on the course of treatment and prognosis.
3. Identifying variables influencing the prognosis of patients with PC and body mass index (BMI) ≥ 25 kg/m2. Analysing BMI ≥ 25 kg/m2 influence on the course of treatment and prognosis.
4. Characterising patients with PC and concomitant malignancy with further survival analysis.
5. Establishing new laboratory parameter to assess the prognosis of patients with PC.

**Material and methods:**

In the study, we included 175 patients with pancreatic ductal adenocarcinoma who were treated with adjuvant or palliative chemotherapy and received more than one course of chemotherapy. Subsequently, for further analysis, patients were subdivided into the following groups:

1. Patients with DM *vs.* patients without DM (non-DM).
2. Patients with HTN *vs.* patients without HTN (non-HTN).
3. Patients with BMI ≥ 25 kg/m2 *vs.* patients with BMI < 25 kg/m2.
4. Patients with concomitant malignancy *vs.* patients without concomitant malignancy.

The study was designed in retrospective character. The analysed data encompassed demographic variables, clinical variables, pathological variables, treatment data, laboratory findings before the first course of chemotherapy, survival, and progression time.

By performing receiver operating characteristic curve (ROC curve) analyses, we established laboratory parameter rated before the first course of chemotherapy to assess prognosis – C - reactive protein/lymphocyte ratio (CLR). Statistical analysis using appropriate tests was conducted. Results were regarded as significant with a p-value of ≤ 0.05.

**Results:**

Study no. 1: Patients with DM *vs.* patients without DM.

DM was diagnosed in 42.3% of all patients with PC. Patients with DM had significantly higher median overall survival (OS) than those without (22 months *vs.* 18 months, p < 0.050). The analysed group was further subdivided into a group receiving adjuvant chemotherapy and a group receiving palliative chemotherapy. Longer survival was confirmed only in the palliatively treated group (18 months *vs.* 13 months, p < 0.034). Patients with DM were more often diagnosed with HTN (p < 0.024), had lower CLR levels (p < 0.050), and less often suffered from neutropenia as a side effect of adjuvant chemotherapy (p < 0.034). Tumour location in the pancreatic head (p = 0.050), lack of nodal involvement (p = 0.020), level of carcinoembryonic antigen (CEA) ≤ 5ng/mL (p = 0.019), C-reactive protein (CRP) ≤ 5mg/L (p < 0.001) and CLR ≤ 1.8 (p = 0.001) were significantly associated with longer OS. In the multivariate analysis, CRP level ≤ 5mg/L was the strongest predictor of survival (p < 0.001).

Study no. 2: Patients with HTN *vs.* patients without HTN.

HTN was diagnosed in 52.6% of all patients with PC. No significant difference in OS between non-HTN and HTN groups was confirmed. Patients with HTN were more likely to be older (66.3 *vs.* 61.0; p < 0.001), have DM (p = 0.033), and be diagnosed without distant metastases (p = 0.005). Higher BMI (p = 0.002), usage of angiotensin-converting-enzyme inhibitors/ angiotensin II receptor blockers (ACE-I/ARB) (p = 0.003), diagnosis of DM (p = 0.003), and CLR ≤ 1.8 (p = 0.013) were associated with longer OS. Usage of ACE-I/ARB was the strongest predictor of survival (0.034).

Study no. 3: Patients with BMI ≥ 25 kg/m2 *vs.* patients with BMI < 25 kg/m2.

Of 175 patients with PC, 56 (32.0%) were overweight or obese. No significant difference in OS between BMI ≥ 25 and BMI < 25 groups was established. Patients with BMI ≥ 25 kg/m2 were more likely to have an autoimmune disease, especially chronic lymphocytic thyroiditis (p = 0.020), metastases in 4 or more lymph nodes (N2) (p = 0.041), tumour size between 2 and 4 cm (T2) (p = 0.022) and experience neutropenia as a side effect of palliative chemotherapy (p = 0.014). Higher BMI was associated with longer survival (p = 0.021), whilst CRP level > 5 mg/L with shorter survival (p = 0.025). In further analysis, BMI was confirmed as the strongest predictor of survival (p = 0.021).

Study no. 4: Patients with concomitant malignancy *vs.* patients without concomitant malignancy.

Fifteen patients enrolled in this work accounted for 5.3% of all analysed cases. All patients were presented with PC and other primary malignancies, encompassing breast (5), ovarian (3), colorectal (3), prostate (2), hepatocellular (1) carcinomas, and thymoma (1). In most cases of first primary cancers, complete response or remission was achieved. The median OS was 75.0 months from the diagnosis of the first primary cancer and 14.0 months from the second primary cancer diagnosis. There was no significant difference in progression-free survival (p = 0.440) and OS (p = 0.280) between patients with and without a history of other malignancies.

**Conclusions:**

1. DM is prevalent among patients with PC. It is associated with longer median OS, especially in the palliatively treated group. Further studies are required to discover the exact mechanism associated with this phenomenon. Tumour localisation in the pancreatic head, CEA ≤ 5 ng/mL, CRP ≤ 5 mg/L and CLR ≤ 1.8 are prognostic factors associated with longer survival.
2. Regarding HTN, the disease itself does not influence survival, but the use of ACE-I/ARB is correlated with better survival. Other prognostic factors associated with longer OS are higher BMI, the coexistence of DM and CLR ≤ 1.8.
3. Higher BMI is the strongest prognostic factor associated with longer survival in patients with BMI ≥ 25 kg/m2 and PC. Obese patients slower develop cachexia and, as a result, might better tolerate and respond to oncological treatment.
4. Second primary tumours do not affect the OS of patients with PC.
5. CRP to lymphocyte ratio can be a feasible prognostic factor.