Pancreatic cancer is one of the most aggressive malignant diseases due high rate of recurrence and the lack effective medical therapy. Surgery remains the only option for curable treatment but unfortunately, less than 20% of patients are eligibles at the time of diagnosis therefore identifying the risk factors represent a big step for cancer research. Pancreatic cancer is frequently associated with diabetes or glucose intolerance. There are two hypotheses at the base of this observation: either the diabetes cause pancreatic cancer or is a consequences of the cancer. In these theses we studied the patients diagnosticated with pancreatic cancer and with diabetes mellitus type 2. A total of 256 pancreatic cancer cases were identified and 71 patients had diabetes mellitus and 21 patients had glucose intolerance. Mean age 62.2 years, 81% cases were male and in 71% cancer originated form the pancreatic head. In 51.4% cases the diagnosis was in stage IV of the disease. Patients with pancreatic cancer and diabetes mellitus had reduced survival compared with those without diabetes but the difference was not statistically significant. Diabetes mellitus is associated with a decreased survival among patients with pancreatic cancer and reveal a link between chronic glucose intolerance and pancreatic cancer survival. The complex relationship between pancreatic cancer and diabetes requires more clinical research in order to developed new therapeutical posibilities.

Keywords: pancreatic cancer, diabetes miltius, survival, glucose intolerance
Experimental part

We evaluated patients with pancreatic cancer and diabetes mellitus or glucose intolerance admitted in our Surgical Unit between January 1, 2012 and December 31, 2016. We included in this study only the patients with clinic, imagistic, laboratory and morphopathological diagnosis of pancreatic neoplastic disease. The socio-demographic data related to age, gender, residence, smoking habits, and family and personal medical history and treatment were collected from hospital database.

The data were processed using IBM SPSS Statistics and the statistical analysis was made with Anova, Student’s T-test, chi-square test and Fisher test in order to assess the quantitative and qualitative variables between the collected data. The result were considered statistically significant if p was less than 0.05 and a 95% confidence interval.

Results and discussions

A total of 256 pancreatic cancer cases were identified and 71 patients had diabetes mellitus and 21 patients had glucose intolerance. Mean age 62.2 years, 81% cases were male and in 71% cancer originated from the pancreatic head. In 51.4% cases the diagnosis was in stage IV of the disease (table 1).

In the selected group, the patients had in 29% localized disease, 19.1% had locally advanced disease, and 51.4% had metastatic disease. The median survival times were 23 months for patients with localized, 13 months for those with locally advanced and 7 months for those with metastatic disease. By the end of the follow-up 91% of patients had died.

Patients with pancreatic cancer and diabetes mellitus had reduced survival compared with those without diabetes but the difference was not statistically significant. The glucose intolerance diagnosed prior or at the time of cancer confirmation had no impact in patient prognostic and the pancreatic resection had no influence in postoperative glycemic levels.

Cancer represents one of the most important pathological manifestations at worldwide level, being characterized by an extremely complex etiology, inducing highly diverse associated complications of physiological, metabolic or biochemical nature [11-15].

In the pathology of tumors, there are several reasons in favor of immunology. Spontaneous regressions of malignant tumors and of their metastases have been reported, as well as an increased incidence of neoplasia in immuno-depression. One of the main functions of the immunity system in neoplastic pathology consists in the detection and purging of new tumoral cells. The paradox of immunology is that, often, the immunitary system favors tumor development rather than its inhibition [16]. Blocking of normal cell mechanisms of apoptosis, followed by uncontrolled proliferation, leads to the formation of cancer cells populations [17].

Pancreatic cancer is a life-threatening disease with an overall 5-year survival rate about 6% and a median survival rate that varies from approximately 2 years in resectable disease to few month in case of locally advanced or metastatic disease [18]. Because the advance stage in time of the diagnosis only about 20% of patients are candidates for surgery [2].

In order to reduce the mortality associated with this disease the key is an early diagnosis, treat the precursor disease and identifying the risk factors that are modifiable [2, 19]. The goal is to identify the high-grade precursor lesions and/or early invasive pancreatic cancer in order to obtain the most benefits from surgical resection [20]. The findings of definitive biomarkers are not available, but further research will hopefully lead to the identification of biomarkers that will potentially lead to early identification to invasive growth [19]. Butler et al. [21] studied the effect of diabetes mellitus on pancreatic cancer in this research of the expression of the neoplastic markers cytokeratin and Ki67 in pancreatic ductal epithelia from 45 human autopsy and nine surgical pathology specimens. They observed that in obese diabetics the duct epithelial replication was increased compared with nondiabetic subjects indicating an effect of obesity and long-standing diabetes on the replication rate and therefore in development of pancreatic cancer. In the surgical specimens or in the non-tumor tissue surrounding cancer cells were observed even higher rates of replication markers implying the role of these factors in carcinogenesis [21].

Despite the latest studies indicate that diabetes mellitus is associated with an increased risk of pancreatic cancer, the pathological mechanism of diabetes-related have not been yet elucidated. It seems that glucose resistance and compensatory hyperinsulinemia represent the me mechanisms associated with diabetes and development of pancreatic cancer and several epidemiological studies revealed also an increased risk for other malignancies.

For the local disease the treatment implied tumor resection and lymphadenectomy.

In two patients with locally advanced stage due to oncological reasons was required resection of a totally replaced common hepatic and reconstruction using a reversed splenic artery.

For the other cases of locally advanced or metastatic disease were performed palleative procedures in order to treat the jaundice, duodenal obstruction or pain consequently to celiac trunk invasion.

### Table 1

| Patient characteristic |         |
|------------------------|---------|
| Mean age (SD), years   | 62.2    |
| Males, n (%)           | 207 (81)|
| ASA classification n (%) |     |
| I                      | 36      |
| II                     | 40      |
| III, IV                | 15      |
| Co-morbidity, n (%)    |         |
| Cardiac                | 28 (11) |
| Hypertension           | 46 (18) |
| Pulmonary              | 10 (4)  |
| Diabetes mellitus      | 71 (28) |
| Glucose intolerance    | 21 (4,7)|
| BMI index mass (mean)  | 25.7    |
| Tumor location, n (%)  |         |
| Head                   | 182 (71)|
| Body                   | 16 (6.4)|
| Tail                   | 50 (22.6)|
| Cancer stage, n (%)    |         |
| Localized              | 76 (29.5)|
| Locally advanced       | 49 (19.1)|
| Metastatic             | 131 (51.4)|
| Median survival, months|         |
| Localized              | 23      |
| Locally advanced       | 13      |
| Metastatic             | 7       |
| Overall survival       |         |
| With diabetes mellitus | 10.9    |
| Non-diabetes mellitus  | 10.6    |

p-value 0.53
including carcinomas of the breast, prostate, colon, and kidney [22, 23].

Hyperglycaemia is an initiating event leading to a series of metabolic changes that may originate from increased oxidative stress [24]. The hyperglycaemia induced by increased oxidative stress and receptor for advanced glycation end products (RAGE) activation increases the activation of transcription factor-beta (NF-βB) in endothelial and vascular smooth muscle cells.

This transcription factor regulates the expression of the genes encoding a number of mediators of atherogenesis such as leukocyte-cell adhesion molecules and chemoaatractants that recruit lymphocytes and monocytes into the vascular wall [25]. Also, oxygen free radicals (superoxide anion, hydroxyl radical etc) produced in excess stimulate lipid peroxidation of the polyunsaturated fatty acids forming, thus, in excess, lipid-peroxil radicals [26].

Many studies indicated that 25% to 50% of the patients diagnosed with pancreatic cancer will have developed diabetes within less than 3 years prior the malignancy ascertainment and suggest that diabetes mellitus might be a biomarker of early-stage PC [24]. The new-on-set diabetes is not a individual predictor of pancreatic cancer and can be the only indication for radiological or endoscopic screening, because about 98% of patients diabetes will never develop pancreatic cancer and the screening did not result to be either practical or reliable as an early detection method [27, 28].

A meta-analysis of 20 studies about the relation between pancreatic cancer and diabetes examined by Everhart et al. [29] identified a relative risk from of 2.1 for diabetes with a duration of at least, 1 year prior to neoplastic diagnosis and 2.0 for diabetes with a duration of at least 5 years and the conclusion was that cancer could be added to the list of complications of diabetes.

We observed a small difference in survival for patients with diabetes compared with those without diabetes [30-32]. The conclusion was that cancer could be added to the list of metabolic changes that may originate from increased oxidative stress [26].

Conclusions

The mechanism implicated in the association of pancreatic cancer and diabetes is not completely elucidated but can offer new pathways for therapeutic opportunity. Diabetes mellitus was associated with a decreased survival among patients with pancreatic cancer and reveal a link between chronic glucose intolerance and pancreatic cancer survival. The complex relationship between pancreatic cancer and diabetes requires more clinical research. Also reducing the risk of pancreatic cancer might be obtained by prevention and treatment of diabetes and early detection of tumors in resectable stages.

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