

STATEMENT
by Assoc. Prof. Dr. Nikolay Vasilev Belev, MD
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on the dissertation

Features of exocrine pancreatic function after duodenopancreatic resection due to adenocarcinoma

to: Dr. Nikolay Veselinov Nikolov

for the award of the scientific and educational degree "Doctor" in the scientific specialty "General Surgery"

Scientific supervisor: Assoc. Prof. Dr. Plamen Chernoploski, MD

The dissertation has been discussed and approved for public defense by the Department Council of the Department of Surgical Diseases, Medical University - Varna, with a report of the Department Council entry No. 102-1395/05.06.2025, and a faculty council report entry No. 41/16.06.2025. According to Order P-100-403/16.06.2025 of the Rector of the Medical University-Varna, I am appointed as a member of the scientific jury for the dissertation defense.

The materials presented on paper and electronic media meet the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria (ADRB) and the Regulations on the Development of the Academic Staff at Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

1. General Presentation of the Doctoral Student

Dr. Nikolay Veselinov Nikolov was born on July 19, 1981, in Varna. He completed his secondary education at the humanitarian high school "Konstantin Preslavski" in Varna in 2000. In 2006, he graduated with a Master of Medicine degree from the Medical University of Varna. In 2013, he defended his specialty in General Surgery. From 2014 to 2015, he served as the Head of the Surgical Team at the Surgery Clinic of St. Anna Hospital in Varna. He worked as a surgeon at the same clinic from 2015 to 2022. Since 2022, Dr. Nikolay Nikolov has been the Head of the Surgical Team at the Surgery Clinic of St. Anna Hospital, Varna.

2. 2. Relevance of the Topic

The biology of pancreatic cancer, along with late diagnosis and the lack of effective screening tools for early detection, are key reasons for the poor prognosis (7%-10% overall survival). Pancreatoduodenectomy is the only treatment offering potential cure for patients with adenocarcinoma of the pancreatic head, though the procedure is associated with high postoperative morbidity rates of 18-52% and perioperative mortality up to 4%. The combination of major surgical intervention and limited expected survival makes quality of life a crucial consideration for these patients. Postoperative complications significantly contribute to the deterioration of this quality of life after duodenopancreatic resection for tumors. Pancreatic exocrine insufficiency is linked to deficiencies in micronutrients and fat-soluble vitamins. Enzyme replacement therapy is associated with improved survival, as supported by numerous studies. Due to the limited and sometimes conflicting research on the dynamics of pancreatic exocrine secretion following pancreaticoduodenectomy and the lack of comprehensive analysis regarding their relationship with reconstructive techniques, it is scientifically justified to explore these areas in detail. Therefore, the topic's relevance is clear.

3. Knowledge of the Problem

The analysis of 121 duodenopancreatic resections (averaging approximately 24 procedures annually) indicates sufficient workload for in-depth study and research led by Dr. Nikolay Nikolov. The perioperative assessment of pancreatic exocrine function is underrepresented in current literature. Studies examining the exocrine function based on different reconstruction methods have yielded conflicting results, underscoring the need for further investigation. The long-term effects of pancreatico-gastroanastomosis on digestion physiology are insufficiently explored. Various studies assessing the relationship between anastomotic techniques and early postoperative complications have produced mixed outcomes. The structural and functional integrity of the pancreatic duct after resection requires further clinical assessment. Fecal elastase 1, a marker directly reflecting pancreatic secretory capacity, offers the highest statistical reliability. Despite extensive understanding of pancreatic adenocarcinoma biology, the direct impact of enzyme deficiency on tumor growth and metastasis remains poorly studied. The conclusions drawn from the existing literature reflect detailed analysis and demonstrate the candidate's strong knowledge base, forming a solid foundation for the dissertation.

4. Study methodology.

A retrospective cohort study was carried out over six years (2017–2022) at the Surgery Clinic of Varna Hospital at the Military Medical Academy. During this period, 121 duodenopancreatic resections were performed for neoplasms, and 92 patients with adenocarcinoma of the pancreatic head were selected for analysis. Patients were excluded if they did not meet the study's inclusion and exclusion criteria. Selection was based on age, sex, tumor size, histological type, and resection margin. Clinical and laboratory methods evaluated the preoperative general condition. Of particular importance was the stratification of preoperative exocrine pancreatic insufficiency according to fecal elastase-1 levels, as well as impairment of exocrine pancreatic function in patients with a dilated pancreatic duct (>3mm) identified through imaging techniques such as spiral computed tomography and magnetic resonance imaging. Surgical methods involved studying pancreatic drainage based on the reconstruction type, including pancreatojejunostomy and pancreatogastrostomy. The technical details of both techniques are described thoroughly. A standardized surgical approach is vital for reducing postoperative pancreatic fistula, which is the most significant postoperative complication and also influences the development of postoperative exocrine pancreatic insufficiency. Postoperative complications were classified according to the ISGPS and Dindo-Clavien systems. For this study, cases of fistula types B and C, hemorrhage types B and C (both intraluminal and extraluminal), intra-abdominal abscesses, acute postoperative pancreatitis, and impaired gastric emptying were examined. The frequency of these complications across both anastomotic techniques was analyzed. Special attention was given to complications related to pancreatic anastomosis insufficiency and postoperative acute pancreatitis, as they are expected to lead to atrophy of the pancreatic remnant.

5. Evaluation of the dissertation work.

The dissertation was approved and scheduled for defense at a meeting of the "Department of Surgical Diseases" at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna on 04.06.2025. It spans 118 pages, includes 39 figures and 43 tables. The bibliography lists 258 references, with 5 in Cyrillic and 253 in Latin. The research was conducted at the Department of Surgery at the Sofia Hospital of the Military Medical Academy and at an external clinical reference laboratory. The doctoral student works at the Clinic of Surgery at St. Anna Hospital in Varna.

The dissertation clearly defines the goal of studying exocrine function after pancreaticoduodenal resection for neoplasms, along with postoperative survival, quality of life, the relationship between maldigestion, tumor growth, and metastasis. It also examines the correlation between different reconstructive techniques (pancreatogastrostomy and pancreaticojejunal anastomosis) and enzyme activity.

To achieve this goal, five specific tasks are outlined. Six conclusions have been drawn that logically follow from these tasks.

The results are presented in a suitable analytical format. In the descriptive analysis, the average age of the patients was determined to be 66 years, which aligns with data from the literature. Mechanical jaundice was the first sign of the disease in 82.60% of patients. This led to hyperbilirubinemia, which increased in severity and became one of the most common symptoms in the study. In 29.68% of icteric patients, impaired coagulation was observed, resulting from decreased liver synthetic function. In 7.81% of patients, impaired renal function was recorded, showing deviations in blood gas analysis and ionogram. Preoperative biliary drainage was performed in 30% of the patients, causing cholangitis in two-thirds of them, most often due to gram-negative microorganisms from the Enterobacteriaceae family. These findings are similar to published data. Cholangitis was identified as an independent risk factor for postoperative complications after Whipple's procedure in the studied patient group. Early etiological diagnosis and definitive surgical treatment in icteric patients could decrease the risk of these complications.

The clinical signs of pancreatic carcinoma are often masked by underlying chronic pancreatitis. Sixty percent of the patients studied had underlying chronic pancreatitis, confirmed histologically after surgery. Conditions such as exocrine insufficiency, chronic inflammation, and often concomitant diabetes are considered factors contributing to poor pancreatic reserve before surgery.

Patients in the study were divided into three groups based on their preoperative exocrine insufficiency level to assess in which group the VDR receptor mechanism (lack of fat-soluble vitamin D) might be a possible cause of tumor development. Results showed 69.6% with exocrine insufficiency and vitamin D deficiency, suggesting that the VDR receptor mechanism could play a role in initiating the neoplastic process in this region of the study. Weight loss was reported as the second most common symptom in 73.91% of patients, often accompanied by pancreatic exocrine insufficiency in 82.4%.

Imaging study results indicated that in 74.2% of cases with a main pancreatic duct diameter over 3 mm, a "hard" pancreas was observed during surgery, and 96% showed exocrine pancreatic insufficiency. This supports the use of duct dilation as a reliable preoperative indicator for planning the appropriate method of pancreatic reconstruction after duodenopancreatectomy. Patients with significant weight loss demonstrated pancreatic atrophy and increased duct diameter, correlating with exocrine deficiency and nutritional insufficiency. Based on these findings, it can be concluded that pancreatic atrophy degree and duct diameter, identified via scintigraphy, are reliable indicators of underlying exocrine insufficiency due to chronic pancreatitis.

Surgically, a significantly higher occurrence of fistula type B in patients undergoing pancreatogastrostomy (14%) compared to the PYA group (7%) warrants discussion. Interestingly, no pancreatic fistula type C was observed in the same group, despite a higher incidence of postoperative pancreatitis and intra-abdominal abscesses. Conversely, 7% of

cases with pancreaticojejunal anastomosis required reoperation due to fistula type C. Notably, 73% of these patients had a solid pancreas. Factors influencing these outcomes, such as pancreatic duct size, pancreatic consistency, fat infiltration, blood loss, surgical technique variations, and external drainage, should be considered. The limited number of patients with pancreaticojejunal anastomosis also affects the findings. It is logical that a higher rate of severe bleeding complications, associated with pancreaticojejunal anastomosis, leads to fistula type C formation.

In patients with pancreatic anastomosis insufficiency, 60% of those with fistula type B developed postoperative pancreatic atrophy as shown by scintigraphy. All patients with fistula type C exhibited pancreatic atrophy. These groups showed impaired exocrine function post-surgery, highlighting the need to explore ways to reduce complications. Preoperatively, exocrine insufficiency was observed in 69.6% of the examined patients, postoperatively this percentage dropped to 60.9%. These data confirm the working hypothesis of preservation of exocrine function, comparable preoperatively and in the postoperative period. To a large extent, this is due to underlying chronic pancreatitis and basally depleted secretory reserve of the gland, therefore, removal of tumor obstruction of the pancreatic duct does not lead to complete normalization of the exocrine capacity of the gland. Exocrine pancreatic function significantly worsens after mucosation of the pancreatic duct in 35.7% of patients with pancreatogastro anastomosis. This is confirmed by low levels of fecal elastase-1. Gastroscopic mucosal resection after mucosal obliteration of the pancreatic duct was first reported in our country as a method to improve pancreatic exocrine secretion. The parallel analysis of exocrine function over the one-year period shows a tendency to preserve the preoperative levels of exocrine function postoperatively. Within the study, patients undergoing pancreaticogastroanastomosis showed a lower relative proportion of severe exocrine insufficiency compared to those with pancreaticojejunostomy. There is a tendency to maintain lower mortality rates in the PGA group. A strong correlation ($r = 0.568$; $p = 0.001$) exists between mortality and exocrine insufficiency in the studied groups. The high percentage of postoperative mortality in the second month (11% in both groups) and the high one-year mortality rate (89%) in the group after pancreaticojejunostomy are noteworthy. Regarding the influence of exocrine function on the frequency of local recurrences, the analysis shows that in 71.6% of the studied patients with severe exocrine insufficiency, oncological disease progression was observed during follow-up. In the group with moderate exocrine insufficiency and normal residual pancreatic parenchyma, disease progression occurred in 56.9% of cases. Given these significant results, a hypothesis arises about the impact of normal digestive function on the progression of pancreatic carcinoma. The discussion follows the structure of the Results chapter and this allows the reader to gain clear impressions of the place of the author's results among the data of the world literature. One of the radiological criteria for chronic pancreatitis in the literature is the size of the pancreatic duct over 3 mm. In this study, the correlation between this indicator and the presence of exocrine insufficiency was traced. It was found that 96.8% of patients with a pancreatic duct diameter of over 3 mm had preoperative fecal elastase levels below 200 µgr. This result makes it possible to predict exocrine function by measuring the main pancreatic duct. The relationship between the consistency of the pancreatic parenchyma and a dilated pancreatic duct of over 3 mm was additionally studied. In 74.2% of the studied cases with a dilated main pancreatic duct, a "hard" pancreas was found, and the subjective experience of the surgeon here would influence the statistical results (it is absolutely illogical to perform a reconstructive pancreatic anastomosis "...according to the surgeon's preferences"). With a high degree of

reliability, the intraoperative assessment of pancreas consistency aligns with the results of imaging diagnostics.

6. Literature Review

The literature review includes 258 sources, of which 5 are in Cyrillic. It analyzes numerous modern meta-analyses and randomized studies related to the various focus areas of the candidate's work, making it sufficiently comprehensive and in-depth.

7. Abstract

The abstract spans 88 pages and contains all necessary information for summarizing and describing the dissertation.

8. Contributions

The idea of dynamic monitoring of exocrine function after duodenopancreatic resection, including the impact of complications on the functional capacity of the residual pancreas, as well as tracking the relationship between pancreatic functional capacity and physical parameters affecting quality of life after duodenopancreatic resection, is of significant value. Gastroscopic mucosal resection following mucosal obliteration of the pancreatic duct was first reported in our country as a method to improve pancreatic exocrine secretion.

9. Conclusion

Dr. Nikolay Nikolov is a surgeon with over 10 years of experience in his specialty, including extensive work in emergency and planned oncological surgeries. The proposed dissertation holds scientific, practical, and applied value, demonstrating the importance of assessing pancreatic exocrine insufficiency and exploring its influence. Organizing prospective and especially randomized studies within surgical procedures is challenging due to factors such as the diverse patient population (including anatomical differences, cancer stages and biology, comorbidities, and malnutrition) and the involvement of multiple surgeons applying various surgical techniques. In this regard, any study covering surgical methods and postoperative monitoring—both short-term and long-term—is highly commendable. I respectfully propose to the esteemed Scientific Jury that Dr. Nikolay Nikolov be awarded the academic and scientific degree of "DOCTOR" for his work on this topic.

Plovdiv
28.08.2025

Ass. Prof. Nikolay Belev-PhD, FACS

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679