

To the Chairman of the Scientific Jury  
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**REVIEW**

by

Prof. Dr. Pencho Tonchev Tonchev, D.M.

Head of Department "Nursing Surgical Care"

Faculty of Public Health, MU-Pleven

Regarding: Public defense of dissertation work for obtaining educational and scientific degree "doctor" on the topic: "Peculiarities of exocrine pancreatic function after duodenopancreatic resection for adenocarcinoma", developed by Dr. Nikolay Veselinov Nikolov, doctoral student at the Department "Surgical Diseases" at Medical University "Prof. Dr. P. Stoyanov" - Varna, with scientific supervisor Assoc. Prof. Dr. Plamen Chernopolski, D.M.Sc. and scientific consultant Prof. Dr. Daniel Kostov, D.M.Sc.

This review is prepared in accordance with the provided Dissertation and abstract, as well as the set of electronic documents.

Dr. Nikolay Veselinov Nikolov graduated in Medicine from MU-Varna in 2006 and specialised in surgery from 2008 to 2013 at MBAL "St. Anna" in Varna. Between 2015 and 2022, he worked in the surgical clinic of MMA-Varna, and since 2022, he has returned to MBAL "St. Anna" Varna and enrolled in doctoral studies in general surgery at MU-Varna in 2024. He has completed his individual plan, passed the candidate minimum and published 3 articles on the topic. He has courses and specialisations in the field of liver and laparoscopic surgery. The topic of the dissertation work reflects his specialised interests in pancreatic surgery and oncology.

The attached "Declaration for registration of profiles in scientific databases" indicates the author's profile in "Google Scholar" <https://scholar.google.com/citations?user=QDdD93QAAAAJ&hl=bg>, which contains multiple publications on topics such as construction, economics, physics, and acoustics, but not a single one from medicine. It is the author's responsibility to clean the profile of foreign publications!

The scientific work presented for evaluation, "Peculiarities of exocrine pancreatic function after duodenopancreatic resection for adenocarcinoma", is developed in accordance with the requirements for obtaining the scientific and educational degree "doctor", illustrated with multiple figures and tables and has a total volume of 133 pages, distributed as follows:

I. Literature review - 34 pp. II. Aim and objectives - 1 p. III. Materials and methods - 9 pp. IV. Results - 49 pp. V. Discussion - 17 pp. VI. Conclusions - 1 p. VII. Conclusion - 1 p. VIII. Contributions - 1 p. IX. Used literature - 15 pp.

## **RELEVANCE OF THE TOPIC**

The relevance of the dissertation work is based on the fact that pancreatic adenocarcinoma ranks fourth as a cause of mortality from oncological diseases with an extremely unfavourable prognosis. Exocrine insufficiency of the pancreas is a significant issue that impacts the quality of life and survival of patients. Despite this, studies on the dynamics of pancreatic exocrine secretion after pancreatoduodenectomy are scarce and contradictory, which makes the present study relevant and necessary.

## **LITERATURE REVIEW**

The literature review, spanning over 34 pages, is systematic and comprehensive. The epidemiology, aetiology, clinical picture and modern diagnostics of pancreatic adenocarcinoma are consistently reviewed. The surgical treatment, including reconstructive techniques after duodenopancreatic resection, is presented in detail. Special attention is paid to the physiology of normally functioning pancreas and the effects of pancreatoduodenectomy on exocrine function. The literature analysis is modern and includes 258 sources, of which 5 in Cyrillic.

## **AIM AND OBJECTIVES**

The stated aim "To study exocrine function after pancreatoduodenal resection for neoplasms, postoperative survival, quality of life, the relationship between maldigestion, tumour growth and metastasis, as well as the correlation between types of reconstructive techniques" is ambitious but adequate to the problem. The five objectives for implementation are precise and correspond to the topic of the dissertation work.

## **MATERIALS AND METHODS**

The study included 92 patients with adenocarcinoma of the pancreatic head who underwent surgery over 6 years (2017-2022) in the Department of Surgery at MBAL-Varna, MMA. The inclusion and exclusion criteria are clearly defined. The methodology used is appropriate for the purposes of the study, including the assessment of performance status, haematological and biochemical parameters, imaging diagnostics, and laboratory analysis of exocrine function through faecal elastase-1.

## **RESULTS**

The results of the dissertation research are presented in detail and systematically over 49 pages. The analysis of 92 patients with adenocarcinoma of the pancreatic head reveals significant findings regarding demographic characteristics, clinical manifestations and surgical results.



From a demographic perspective, the average age of patients is 67.8 years, with a minimal difference in gender distribution: 54.3% women and 45.7% men. Mechanical jaundice is established as the most common first symptom in 74.4% of cases, with 82.6% of jaundiced patients having it as the first clinical manifestation of the disease. In 30% of patients with mechanical jaundice, preoperative biliary drainage was performed, with cholangitis developing in 70% of stented patients.

A significant finding is the frequency of underlying chronic pancreatitis in 60.5% of the studied cases, although only 19.2% had been previously diagnosed with this disease. Diabetes mellitus is found in 53.5% of patients preoperatively, with the frequency reaching 46.2% in the group with chronic pancreatitis.

Preoperative assessment of exocrine function reveals impaired function in 69.6% of cases, with faecal elastase-1 levels below 200 µg/g. Weight reduction is observed in 73.91% of patients, with 82.4% of them having it combined with severe exocrine insufficiency with FE-1 levels below 100 µg/g. Clinically manifested maldigestion is registered in 80.8% of patients with impaired exocrine function.

Imaging diagnostic analysis demonstrates a strong correlation between CT criteria for chronic pancreatitis and intraoperative determination of the pancreas as "hard," with statistical significance ( $r = 0.916$ ,  $p < 0.001$ ). In patients with a main pancreatic duct diameter above 3 mm, exocrine insufficiency is established in 96.8% of cases. In patients with CT criteria for pancreatic atrophy, severe exocrine insufficiency is found in 88.5% of cases.

Surgical results show significant differences between the two types of reconstructive techniques. Pancreaticogastrostomy was performed in 63% of patients, with an average operative time of 4.1 hours, while pancreatojejunostomy was used in 37% of patients, with an average operative time of 4.4 hours. Intraoperative blood loss under 500 ml was registered in 84.29% of the PGA group and in 81.52% of the PJA group.

Analysis of complications reveals significant differences between the two techniques. Pancreatic fistula type B develops in 14% of patients with pancreaticogastrostomy versus 7% with pancreatojejunostomy. However, no case from the PGA group develops a type C fistula, whereas in the PJA group, this percentage reaches 7%. Postoperative haemorrhage type C is observed in 4% of PGA cases (exclusively intraluminal) versus 7% in the PJA group (extraluminal). Delayed gastric emptying is found in 32% of patients undergoing pancreaticogastrostomy, compared to 21% in the other group.

The dynamics of exocrine function shows a general tendency to preserve preoperative levels. Preoperatively, exocrine insufficiency is observed in 69.6% of the studied, with this percentage decreasing postoperatively to 60.9%. During the first month, severe exocrine insufficiency is reported in 21.70% of the PGA group, compared to 15.20% in the PJA group. Notably, in 35.7% of patients undergoing pancreaticogastrostomy, coverage of the anastomosis with gastric mucosa

is established, which strongly correlates with the development of severe exocrine insufficiency ( $r = 0.678$ ,  $p = 0.001$ ).

Survival analysis demonstrates a statistically significant difference between the two anastomotic techniques. The mean survival in patients with pancreaticogastrostomy is 9.966 months, compared to 8.067 months with pancreaticojejunostomy, with statistical significance ( $p < 0.009$ ) as determined by the Log Rank test. When analysing the influence of exocrine function, it is established that patients with severe exocrine insufficiency have a mean survival of 6.859 months with PJA versus 7.235 months with PGA.

The study of the relationship between exocrine function and tumor progression reveals that in 71.6% of patients with severe exocrine insufficiency, disease progression is observed compared to 56.9% in patients with moderate insufficiency or normal function. Metastasis and recurrence within the one-year follow-up is found in a total of 39.13% of cases.

Hospital stay differs significantly in the presence of complications. In patients with type B fistulas, the average total stay is 20.67 days, compared to 15.15 days in the control group. For patients with type C fistulas, this indicator increases to 21.75 days. Mechanical jaundice emerges as an independent risk factor, with 92.1% of all complications developing in jaundiced patients.

## **DISCUSSION**

In the "Discussion" chapter, the results are interpreted in the context of existing literature. The author demonstrates good knowledge of the problem and makes valid comparisons with published data. The limitations of the study are acknowledged and the need for prospective studies is emphasised.

## **CONCLUSIONS**

The dissertation research concludes with six main findings that reflect the key insights of the analysis.

The first conclusion emphasises the diagnostic value of imaging criteria for assessing pancreatic function. It is established that CT parameters for chronic pancreatitis and intraoperative consistency of the gland demonstrate high degree of correlation with the exocrine capacity of the pancreas. This finding provides surgeons with the possibility of preoperative assessment of the gland's functional state without the need for invasive studies.

The second conclusion emphasises a specific feature of pancreaticogastrostomy. The finding that in over one-third of patients, coverage of the anastomotic surface with gastric mucosa develops, leading to deterioration of exocrine function, necessitates a recommendation for routine endoscopic follow-up. Mucosal incision in these cases may improve postoperative pancreatic function.



The third conclusion confirms the superiority of pancreaticogastrostomy regarding severe complications. A lower proportion of class C complications, according to the ISGPS classification, is demonstrated, along with a shorter hospital stay and better preservation of exocrine function. These results support the use of this technique in suitable patients.

The fourth conclusion identifies preoperative mechanical jaundice as an independent prognostic factor. Its negative influence on survival is established, which is probably due to impaired liver function and increased frequency of postoperative complications in these patients.

The fifth conclusion reveals the relationship between exocrine function and oncological prognosis. The statistically significant difference in disease progression between patients with severe exocrine insufficiency and those with preserved function suggests a biological role of digestive disorders in tumour biology. This finding has the potential to influence therapeutic approaches.

The sixth conclusion synthesises the relationship between exocrine function and survival. It is established that preserved digestive function after surgery correlates with improved survival and lower mortality levels, which emphasises the significance of functional aspects in oncological treatment.

These conclusions, taken together, outline exocrine function as a key factor in the complex treatment of pancreatic adenocarcinoma, which affects both early postoperative results and long-term prognosis of patients.

## **CONTRIBUTIONS**

The contributions of the dissertation work include the dynamic follow-up of exocrine function in established reconstructions, the determination of the diagnostic value of indirect criteria for assessing pancreatic function, and an analysis of survival as a function of exocrine activity.

## **CRITICAL REMARKS**

Despite the positive aspects of the dissertation work, there are several methodological limitations that reduce the scientific value of the study:

### **Methodological problems:**

The study represents a retrospective cohort study without a clearly defined control group. The term "control group" is often misused to refer to subgroups within the same cohort. Power analysis for determining the required sample size is lacking, as 92 patients over a 6-year period represent a relatively small sample.

Selection bias represents a serious problem - the choice of reconstructive technique depends on "individual preferences of surgeons", which compromises the comparability of groups. A twelve-month follow-up is insufficient for oncological conclusions, and the lack of multivariate analysis does not allow for adequate control over confounding factors.

**Statistical analysis:**

No correction for multiple tests in multiple comparisons is applied. Some subgroups contain too few patients for valid statistical conclusions. Multivariate logistic regression for the identification of independent risk factors is lacking.

**Interpretation of results:**

The author makes overly categorical conclusions based on limited data. For example, the statement that "imaging diagnostic criteria with a high degree of reliability show exocrine capacity" is based on retrospective analysis with present bias. The recommendation for control gastroscopy is based on a frequency of 35.7% in a selected group, which is insufficient as an evidence base.

Cause-and-effect relationships are often assumed based on correlational data, particularly regarding the relationship between exocrine function and tumour progression. The conclusions about the influence on metastasis exceed the possibilities of the retrospective design.

**Structural problems:**

The title does not accurately reflect the study's scope. More appropriate would be "Comparative analysis of reconstructive techniques after duodenopancreatic resection and their influence on exocrine function in patients with adenocarcinoma".

Regarding mortality during the first year, patients with PJA have 80% mortality during the first year, while those with PGA have around 50%!

**RECOMMENDATIONS**

To overcome the mentioned limitations, the following improvements would be necessary: a prospective randomised design with an adequate control group, a power analysis to determine the required sample size, a longer follow-up period (minimum 3-5 years) for valid oncological conclusions, multivariate analysis to control for confounding factors, and a more conservative interpretation of the results.

**CONCLUSION**

Regardless of the mentioned methodological limitations, the dissertation work addresses an important clinical topic and presents interesting observations from Bulgarian clinical practice. The work demonstrates a serious approach to studying a complex surgical problem and can serve as a basis for future prospective studies. The results have practical value for surgeons working in the field of pancreatic surgery.

The bibliographic reference is comprehensive and modern. The presentation is clear and consistent, and the results are presented systematically.

Taking into account the relevance of the topic, the clinical significance of the results and the necessity for development of pancreatic surgery in Bulgaria, despite the methodological

limitations, I express my favourable position for the defense of the dissertation work and recommend to the esteemed members of the scientific jury to support the awarding of the educational and scientific degree "doctor" to Dr. Nikolay Veselinov Nikolov.

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Prof. Dr. Pencho Tonchev, D.M.