

## STATEMENT

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Regarding: Doctoral dissertation for awarding with Educational and Scientific Degree 'PhD' of Dr. Petko Ivanov Karagyozev at the Clinic of Gastroenterology, Acibadem City Clinic Tokuda General Hospital Sofia

According to Order # 481 / 23.12.2019 of Acibadem City Clinic Tokuda General Hospital CEO and the Decision of the Chairman of the Scientific Jury from 2020 I have been appointed to present a statement regarding the doctoral dissertation of Dr. Petko Ivanov Karagyozev on the topic "The place of cholangiopancreatography in the diagnosis and treatment of pancreatobiliary diseases" for awarding with Educational and Scientific Degree 'PhD'.

The possibility of visualization of the gastrointestinal mucosa by gastrointestinal endoscopy gives a great impetus to modern gastroenterology, while narrowing the need for X-ray contrast studies due to their low diagnostic ability. Nowadays, X-ray contrast in gastroenterology is mainly used to represent the biliary tract and pancreatic duct, the so-called Endoscopic retrograde cholangiopancreatography (ERCP). However, this method involves the radiation load for the team, the need for additional equipment and a considerable percentage of complications, incl. post-procedural pancreatitis, infections, perforation, bleeding, etc. In addition, the sensitivity of ERCP to unclear biliary stenoses (one of its main diagnostic indications) according to 2019 data is very low, reaching only 21%, in combination with brush cytology, and the risk of missing specimens is between 11% and 28%. On the other hand, about 15% of choledocholithiasis cases are difficult for extraction. ERCP with respect to pancreatic diseases is with very low sensitivity and specificity. Therefore, any method that helps to visualize the biliary and pancreatic ducts, which at the same time saves procedural time and radiation load of the team is welcome.

Cholangiopancreatography (ChPS) is just such a method. Attempts to visualize the biliary-pancreatic system began more than 30 years ago, but have become more widespread in the clinical practice in the recent years with the development of digital technologies in endoscopy. Various platforms have been described in the literature, but the following two types seem to be mainly distinguished: "mother-baby" type and direct retrograde cholangioscopy. The main indications are: unspecified biliary stenoses, gallstone disease, pancreatic concretions, evaluation of IPMN and some intervention procedures, such as: hemostasis, polypectomy, tumor ablation, etc.

Data in this field are still being accumulated in the world literature, with the total number of publications not exceeding 100. Recommendations of major global endoscopic companies are not yet available, incl. the European, American and Japanese scientific societies. There are no publications in this field in Bulgaria, and at the moment there is only one center with equipment for cholangiopancreatography - where the doctoral student presenting his scientific work practices. All this proves the relevance of the topic.

The author has conducted an in-depth literature review of over 200 sources, most of which are from the last 5-6 years. What makes an impression is the good scientific style, the detailed knowledge of the problem, the various endoscopic platforms, tools, indications for the application of the respective techniques, their advantages and disadvantages. The largest and fundamental meta-analyses citing the novelty of the method, as well as a critical analysis of its ambiguities, are quoted. It addresses:

1. 1. Historical aspects of the emergence and refinement of cholangiopancreatography equipment.
2. 2. Cholangiopancreatography techniques and platforms.
3. 3. Indications for cholangiopancreatography.
4. 4. Clinical application of cholangiopancreatography.
5. 5. Complications with their prevention and treatment.

It is obvious that cholangioscopy contributes to the differentiation of malignancies from benign stenosis with very good sensitivity, specificity, positive and negative predictive power. The combination with biopsy and chromoendoscopy further increase the efficiency of the method. However, there is variability in the sensitivity and specificity of targeted biopsies, which can reach up to 15%. Up to now, 2 generations of ChPS platforms are being used, according to the data cited, the second generation SpyGlass DS has the advantage. Particularly interesting is the fact that ChPS provides more accurate localization of cholangiopancreatic tumors and is able to alter surgery in one third of patients. In almost ½ of patients with post-transplant biliary complications, it has shown an advantage over conventional ERCP. However, one of the most important benefits of the method is in terms of improved visualization, the possibility of lithotripsy, and hence an increase in the clearance rate of the biliary tract from concretions. Better effect is also achieved with regard to cannulation of difficult strictures, tumor ablative therapy, possibility for early diagnosis of premalignant lesions, etc. Visualization of the cholangiopancreatic system gives possibilities for the emergence of different classifications, for example for the differentiation of malignancies from benign lesions, etc. However, there is a low percentage of agreement between researchers, indicating that the method is new, needs more data and refinement, and gives the opportunity for further research.

After analyzing the available data, the doctoral student points out the unexplored areas and those in need of more detailed study.

The purpose of the **thesis and the tasks** of the doctoral dissertation, which are clearly and precisely formulated, are logically derived from the analysis of the literature review.

The study includes 186 patients undergoing 208 cholangiopancreatoscopic procedures. All of them have been through the Invasive Gastroenterology Department, Acibadem City Clinic Tokuda General Hospital Sofia, February 2016 - June 2019. The clinic is the leading reference center for performing highly specialized interventional procedures of the biliary-pancreatic system in the country and the only one having a ChPS platform.

The methods used are described precisely and in detail, and for the first time in Bulgaria interventions are carried out with the most up-to-date ChPS platform - SpyGlass DS. Methods for statistical data processing are diverse and properly selected.

The results obtained are presented in a concise and detailed manner, with 46 figures and 59 tables illustrated. They are in full compliance with the tasks set.

In summary, the most important results show:

1. Biopsy under cholangioscopic control is effective, with high sensitivity and specificity (75% and 100% respectively), positive and negative predictive power. The results are commensurate with other authors, indicating an optimal level of assimilation of the method.
2. In difficult-to-extract ERCP concretions, cholangioscopic-based therapy achieves clearance in over 90% of cases, and in one procedure - in 81.8%. These results are even better than some of the studies cited. The author manages to extract risk factors for failure based on his own experience, namely: concretions greater than 25 mm, history of previous ERCP and duration of index cholangioscopic LL session over 60 minutes.
3. The complications of ChPS are 9.1%, with no deaths reported.
4. Pancreatotomy is particularly effective for clarifying unclear strictures of the common pancreatic duct, diagnosis and preoperative evaluation of md-IPMN, lithotripsy of pancreatic concretions.

The contributions of the doctoral dissertation are mainly with practical application. Of greatest importance are the following:

1. For the first time in Bulgaria experience with the most up-to-date platform for performing CHPS is presented, both in terms of validated indications and some more rare ones, such as iatrogenic lesions missed concretions proximal migrated stents and the like.
2. An algorithm for the behavior of undefined biliary strictures and difficult to extract biliary duct concretions is presented.
3. The results are comparable to those of leading European and American centers.

#### **Critical notes and recommendations for the doctoral dissertation**

It would be good to have a tabular presentation of the results of the cited studies in the literature review, which will make it easier for the referees. Task 1 should not be mentioned, it is part of the literature review, and tasks 3, 4 and 5 should be combined in task 2. Fig. 26 is incorrect, the mean age in the different groups should be represented by a box-plot graph rather than a bar graph.

#### **Conclusion**

As a member of the Scientific Jury, I believe that the doctoral dissertation of Dr. Petko Ivanov Karagyozov on the topic "The place of cholangiopancreatography in the diagnosis and treatment of pancreatobiliary diseases" is extremely relevant and of high scientific value. It meets all the requirements for awarding with Educational and Scientific Degree 'PhD', which is why I give my positive opinion.

23.01.2020 г.

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