STATEMENT

by Prof. Dr. Milena Staneva Staneva, MD, Ph.D, DSc
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Of Doctoral Dissertation: for awarding the Educational and Scientific Degree 'PhD'
Higher education area: 7. Healthcare and sports, Sector 7.1. Medicine
Scientific specialty: "y"
Author: Dr. Petko Ivanov Karagyozov
Doctoral Degree Education Form: Self-directed
Scientific structure: Gastroenterolog Clinic
Topic: "The place of cholangiopancreatoscopy in the diagnosis and treatment of pancreatobiliary diseases"
Scientific supervisor: Prof. Dr. Simeon Stoynov, Ph.D., DSc

1. General presentation of the procedure and the doctoral student

At a meeting of the Scientific Council of the Acibadem City Clinic Tokuda General Hospital (Minutes 30/10/12/2019) and with Order No. 481 / 23.12.2019 of the CEO and the Procurator of the Hospital, I was appointed an internal member of the Scientific Jury in the connection with the doctoral dissertation of Dr. Petko Karagyozov. I am determined to represent Statement.

The procedure is fully consistent with the Law on the Development of the Academic Personnel in the Republic of Bulgaria, the Regulations for the implementation of the Law on the Development of the Academic Personnel in the Republic of Bulgaria at Acibadem City Clinic Tokuda General Hospital, the Rules for the conditions and procedure for acquiring academic degrees and occupying academic positions in Acibadem City Clinic Tokuda General Hospital.

I declare that I have no conflict of interest with the author of the Doctoral Dissertation.

Dr. Petko Karagiozov graduated medicine from the Medical University of Sofia in 2004. From 2006-2011 he is a doctor at the Clinic of Gastroenterology and Hepatology - Military Medical Academy, Sofia, and since 2011 he has been at the Hospital of Tokuda Sofia and from 2015 holds the position of Head of the Department of Interventional Gastroenterology, Clinic of Gastroenterology and Pulmonology; and from 2017 - Head of the Department of Interventional Gastroenterology, Clinic of Gastroenterology. Dr. Karagyozov acquired a specialty in Gastroenterology in 2013 and a certificate of professional qualification in “ERCP and related interventional endoscopic procedures - third level” and in “Interventional and endoscopic abdominal ultrasound” - third level. He has a number of specializations in Gastroenterology, Ultrasound Tomography and Gastrointestinal Endoscopy in Bulgaria, Germany, the Netherlands, Italy, Israel, Austria, etc. Since 2016 he has a Master's Degree in Public Health and Healthcare Management.

He is a member of the Bulgarian Society of Gastrointestinal Endoscopy (ESGE); American Society of Gastrointestinal Endoscopy (ASGE); Bulgarian Scientific Society for Gastroenterology. Member of the Board of Directors of BDGE from 2018.

Cholangiopancreatoscopy Trainer with SpyGlass DS System, Boston Scientific for Eastern Europe.

2. Relevance of the topic

Clinical problems associated with biliary tree and pancreas continue to be a challenge for modern gastroenterologists. Although endoscopic retrograde cholangiopancreatography (ERCP)

has a history of more than 50 years in the diagnosis and treatment of most biliary diseases, the distinction of malignancies with poor diagnostic accuracy, and some of the concretions in the biliary tract, may not be extracted by conventional endoscopic techniques. The introduction of Per-oral Cholangioscopy (PoCh) provides direct visualization of the biliary tract and pancreatic duct for diagnostic and therapeutic purposes, but has poor image quality, difficult to use and high risk for patients. The new Cholangiopancreatoscopy (ChPS) platform overcomes many of the disadvantages. So far, the Department of Interventional Gastroenterology (DIG) at Acibadem City Clinic Tokuda General Hospital is the first and only in the country to put into practice and routinely use ChPS with the SpyGlass DS platform. Dr. Karagyozov's doctoral dissertation is devoted to the application of this method. The topic is extremely relevant from a practical point of view.

3. Knowledge of the problem

The doctoral student knows the status of the problem and appreciates the literary material creatively.

4. Research methodology

The chosen research methodology allows to achieve the set goal and to receive an adequate answer to the tasks solved in the doctoral dissertation.

5. Characterization and evaluation of the doctoral dissertation work and its contributions

Dr. Karagiozov's doctoral dissertation is written in a volume of 186 pages, 48 figures and 59 tables. It is structured correctly and includes the following sections: Abbreviations used and characters -2 pages; Introduction - 2 pages; Literature Review - 52 pages; Purpose and Tasks - 1 page; Material and Methods - 24 pages; Own Results - 59 pages; Discussion - 13 pages, Conclusion - 3 pages, Bibliography - 23 pages. The bibliography includes 222 sources, 4 of them in Cyrillic and 218 in Latin, most of them published in the last 5 years..

The introduction clearly defines the problem and substantiates the purpose of the research in the dissertation.

The literature review is well structured in line with the topics being developed. It is written competently and shows a good knowledge of the issue in its various aspects. It begins with brief historical data. The techniques and platforms for cholangiopancreatoscopy, the indications, the clinical application with advantages and disadvantages, and the complications of the methodology are then reviewed in turn. The literature review concludes with an analysis of the unresolved and controversial issues that warrant the author's conduct of the study.

The purpose of the doctoral dissertation is well formulated in accordance with the topic of the dissertation and the literature review presented. The given tasks, 10 in total, are completely sufficient and have been completed entirely in doctoral dissertation.

The Materials and Methods section describes in detail, 186 patients enrolled, (98 (52.7%) are male, 88 (47.3%) are female, mean age 65.66 ± 13.52 years) , who underwent 208 procedures - per-oral cholangio - and / or pancreatoscopy, respectively, from February 2016 to June 2019. All patients were divided into four groups, depending on the procedure indication: Group 1 - "Difficult concrements", involving 33 patients with a total of 39 procedures performed; Group 2 - “Unspecified biliary strictures”, comprising 73 patients with 86 procedures performed; Group 3 - Missed concrements, comprising 38 patients who underwent 38 procedures; Group 4 - “Others”, comprising 42 patients to who 45 procedures were performed. Clinical, laboratory and instrumental methods have been used - abdominal ultrasound, CT, MRI / MRCP, ERCP, ChPS and pathoanatomical methods. Per-oral ChPS from the Boston-based Spyglass digital system operator - last generation - was used to perform cholangiopancreatoscopies.

Appropriate methods and a modern statistical program (SPSS version 13.0) have been applied to statistical data processing, which guarantees the reliability of the results obtained..

Results and Discussion: The results presented are convincing and clear. The more important ones are the following.

In 9.1% of patients, complications were reported, which were rated as mild and moderate and did not require emergency surgery or intensive care. No procedure-related mortality was

detected. No significant difference was found between the groups. No correlation was observed with age, sex, hematologic and biochemical parameters tested, CRP and comorbidities.

In Group I, complete fragmentation and extraction of all concretions was achieved in a high percentage - 90.9%, with 27 (90%) requiring only one PoCh-LL session. As a predictor of unsuccessful extraction, the dissertation states the concretions of size ≥ 25 mm, a history of previous ERCP procedures and a duration of the procedure longer than 60 min.

In group II, patients with indeterminate stenoses and defects in the delivery that have been previously established by other diagnostic methods. In 75.3% of patients with cholangioscopy, biopsy material was taken, which led to identification of the cause and determination of therapeutic behavior. The diagnostic accuracy of the cholangoscopic image is high - 91.55%. The diagnostic accuracy of the cholangoscopically navigated biopsy is also high - 86.79%, with a sensitivity of 95.00% and a specificity of 87.1%.

In Group III, 'missed concretions', 38 patients underwent endoscopic HolC as a control verification method after navigation treatment of choledocholithiasis or unclear cholangiogram at the end of the procedure. Residual (missed fluoroscopic) concrements were found in 10 patients (26.3%). No significant correlation was found between the incidence of cholangioscopic "missed" concretions and the presence of altered duodenal anatomy, association with distal stricture, and fluoroscopic measured diameter of the common bile duct. No complications and lethality were observed.

Group IV "Others" includes 42 patients with ChPS performed in 35 and PS - in 7 patients with rare or unspecified indications. Indications for ChPS are proximal migration of biliary stent - 10 patients, biliary stricture after unsuccessful cannulation - 4, biliary complications after liver transplantation - at 9, assessment of iatrogenic lesions - 5, planned transpapillary drainage of the gall bladder in connection with acute calculous cholecystosis contraindications for surgical intervention -2, diagnosis of unclear hemobilia - 3. Per-oral pancreatoscopy was performed to 7 patients, with indistinct dilatation / stenosis of the main pancreatic duct in 6 of them. No manipulation complications were observed.

This study by Dr. Karagyozov confirms the high efficacy and safety of ChPS with the SpyGlass DS platform (Boston Scientific Corp, Natick, MA, USA) and the undeniable advantages of the method, mainly in the diagnosis of indeterminate biliary strictures and in endoscopic therapy of "difficult" concretions in the biliary tract. The high image quality, maneuverability, easy setup and use of the system allow it to become an integral part of conventional ERCP and to resort to it early in certain clinical indications. The biggest advantage of ChPS is the ability to directly view and take targeted biopsies. The observed complications - 9.1%, are commensurate with the reported complications of ERCP without ChPS. The dissertation demonstrates that ChPS with SpyGlass DS is highly effective and safe in patients with pancreatic biliary disease.

Conclusions and Contributions: Based on the results obtained, the dissertation logically makes 17 conclusions and recommendations. The contributions are 10 original, scientific, practical and confirmatory contributions. The contributions are related to the introduction of endoscopic cholangiopancreatoscopy in Bulgaria by one operator, as well as the great diagnostic and therapeutic possibilities of the methodology in the pathology of the biliopancreatic system, with comparative safety of patients. The conclusions are consistent with the tasks set.

6. The abstract is presented on 81 pages and reflects the doctoral dissertation.

7. Assessment of publications and personal contribution of the doctoral student

The PhD student has applied 5 publications in refereed journals (one with IF) and four abstracts of papers presented at international scientific forums (published in IF journals). This scientific activity is sufficient to show that the doctoral student is consistent in his scientific activity. Dr. Karagyozov significantly exceeds the minimum required points for the educational and scientific degree "Doctor”.

CONCLUSION

The dissertation work includes scientific, research and applicable into clinical practice results that are original contributions to science by expanding our knowledge in this innovative theme for Bulgaria.

Dr. Petko Karagyozov **is fully compliant** with the current regulatory framework in the country – Law on the Development of the Academic Personnel in the Republic of Bulgaria, the Regulations for the implementation of the Law on the Development of the Academic Personnel in the Republic of Bulgaria at Acibadem City Clinic Tokuda General Hospital, the Rules for the conditions and procedure for acquiring academic degrees and occupying academic positions in Acibadem City Clinic Tokuda General Hospital

Due to the above, I give my positive assessment and strongly recommend to the members of the Scientific Jury to evaluate positively doctoral dissertation "The place of cholangiopancreatoscopy in the diagnosis and treatment of pancreatobiliary diseases" and to award Dr. Petko Ivanov Karagiozov with the educational and scientific degree "Doctor" in the Scientific specialty Internal Medicine.

20.01.2020
Sofia

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