

REVIEW

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Regarding Dissertation "The place of cholangiopancreatostoscopy in the diagnosis and treatment of pancreatobiliary diseases" for awarding the Educational and Scientific Degree 'PhD'

Higher education area: 7. Healthcare and sports, Sector 7.1. Medicine

Scientific specialty: "Internal Medicine"

Author: Dr. Petko Ivanov Karagyozov

Doctoral Degree Education Form: Self-directed

Scientific organization: Scientific Council of Acibadem City Clinic Tokuda General Hospital

Scientific supervisor: Prof. Dr. Simeon Stoynov, Ph.D., DSc

It has been a long-standing dream of medical teams to penetrate and provide direct visibility and opportunity for versatile diagnostic and treatment procedures in one of the most difficult to access areas of the GIT - the biliopancreatic canal system. Diseases in this area are difficult to diagnose, malignancies are diagnosed late, in most cases at the stage of palliative treatment procedures aimed at improving comfort for the rest of these patients' lives. After a long way from the beginning of the last century using different technologies in 1965, the first flexible choledochoscope was designed to allow a direct view of d. choledochus. The methodology continues to evolve, passing in certain intervals through conventional ERCP, mother and baby system, oral retrograde cholangioscopy, mother and baby video cholangioscope, ultra-thin hard guide cholangioscope, pancreateoscopes. The creation of this expensive and relatively inefficient instrument is accompanied by a number of inconveniences for work, poor image, short life of the endoscope, high cost, which is why it is not gaining popularity in routine clinical practice. In 2007 the first generation of the so called Spyglass technology, which overcomes many of the shortcomings of equipment and accessories available so far, and is performed by an endoscopist. The second generation of Spyglass, the so-called Spyglass digital system has been available since 2015 and is the only one oral cholangioscopy system available from a single operator. In Bulgaria, the first cholangioscopy

was performed in the 1980s with a mother-baby fibro-optic cholangoscope at "St. Joanna" General Hospital. The only center currently operating the Spyglass digital system is the Acibadem City Clinic Tokuda General Hospital - Department of Interventional Gastroenterology, led by Dr. Petko Karagiozov.

Dr. Petko Karagyozov graduated from the Sofia University in 2004. He has acquired a specialty in Gastroenterology and holds licenses for qualification in abdominal ultrasound - Level III and gastrointestinal endoscopy - Level III. He has presented a list of publications and participation in congresses and symposia related to his doctoral dissertation. He has specialized in Gastroenterology, Ultrasound Tomography and Gastrointestinal Endoscopy in Bulgaria, Italy, Austria, Germany, Japan, Czech Republic and the Netherlands. He is a member of the European Association of Gastroenterology, the American Association of Gastroenterology, the Bulgarian Scientific Society of Gastroenterology. Educator on the clinical application of cholangiopancreatostomy in Eastern Europe. Fluent in German and English - written and spoken.

The doctoral dissertation is written on 186 standard typescript pages, illustrated with tables and figures, and contains all the necessary sections, recommended for the dissertation for obtaining a Doctor of Medicine degree. It contains 222 literary sources in Latin, published mainly in the last 5-10 years. The author has provided publications and scientific papers related to the dissertation - five articles in refereed journals and four abstracts of papers presented in scientific forums.

The literature review is written in 56 pages in a clear and accessible language with a critical summary of the contemporary view of the subject matter of the study. It includes six chapters with a critical analysis of the topics covered: brief historical data; cholangiopancreatostomy techniques and platforms (ChPS); indications for ChPS; clinical application - advantages and disadvantages; complications and conclusions. The various types of techniques and platforms for ChPS are described in detail, highlighting their advantages and disadvantages, diagnostic value, sensitivity and specificity in targeted biopsies. The major part of the literature review is devoted to the official ChPS indications with additional subsections included: "difficult concretions", "undetermined biliary stenoses", "diagnostic and therapeutic pancreatoscopies", "post-transplant strictures".

The critical review of the LR identifies unresolved and debatable points: the existing limitations and imperfections of the methodology; lack of specific terminology and endoscopic criteria distinguishing tumor processes; lack of

sufficient evidence-based publications for navigated intraductal lithotripsy; the notion of difficult concretions is not specifically defined, as is the location of cholangoscopic lithotripsy. There is no literature data on cholangioscopy in other biliary indications, such as complications after liver transplantation; preoperative staging of biliary neoplasms, extraction of migrating stents, iatrogenic lesions, etc., unclear role of oral pancreatoscopy, in pancreatic neoplasms, issues such as ChPS risks, need for antibiotic prophylaxis, etc. It is these controversial and debatable issues that warrant the author of this study.

The purpose of the study is formulated clearly and the focus is on defining the treatment and diagnostic options based on our own studies, with a view to developing an algorithm for the Bulgarian gastroenterology community that is relevant to the ChPS.

The author has defined 10 tasks that are set specifically to accomplish the goal. In reality, they cover the entire field of ChPS application in routine gastroenterology practice, from the collection and analysis of patient data through indication analysis and ChPS control, grouping of laboratory and instrumental examinations, to important and key technical aspects and judgment for indication, static processing of results, study of registered complications and comparison with other authors, and development of optimal algorithms for clinical practice.

The study includes 186 patients treated at the Endoscopy center for the period 02.02.2016 - 06.06.2019, undergoing 208 procedures - cholangio- and / or pancreatoscopy. The study was retrospective and the patients were divided into 4 groups:

- Group 1 - includes 33 patients and 39 procedures performed (difficult stones)
- Group 2 - includes 73 patients and 86 procedures performed (unspecified stenoses and defects in performance)
- Group 3 - includes 38 patients and 38 procedures performed (missed stones)
- Group 4 - includes 42 patients and 45 procedures performed (other)

Clinical, laboratory, instrumental, morphological, and statistical methods have been used, including control studies to monitor and follow contraindications for individual procedures. Peroral ChPS from a Boston-based Spyglass digital system operator was used to perform cholangiopancreatoscopies. - last generation. In all four groups of patients, the

diagnosis was made on the basis of generally accepted criteria with complete coincidence of the macroscopic local finding with the result of the morphological examination.

The applied set of statistical methods (descriptive statistics, methods of testing statistical hypotheses, statistical evaluation of diagnostic methods imply accurate and correct processing of information, validity, reliability and real analysis in determining the conclusions. Statistical processing was carried out by the technology of the specialized statistical package SPSS Version 13.

In the "own results" section, characteristics of patients by gender, age, comorbidities, hematological and biochemical parameters was performed. In 9.1% of the patients, various complications were assessed as mild and moderate. There was no need for emergency surgery or transfer to an intensive care unit. No statistical significance was found between groups, no correlation with age, sex, hematologic and biochemical parameters tested, CRP and comorbidities. No deaths were reported in connection with the procedures applied. All this speaks for the optimal preparation of the studied patients before the manipulations.

In Group I, complete fragmentation and extraction of all concretions was achieved in 90.9%. No statistically significant correlation was found between the achievement of complete clearance and the number of concretions in the biliary tract, their size, localization, the presence of distal stricture, peri-ampulla diverticulum, surgically altered anatomy and pre-cholangoscopic lithotripsy, one or more ERCP procedures. requiring surgery or further alteration of the treatment approach.

In group II, patients with indeterminate stenoses and defects in adherence established previously by CT, MRCGP, UST and ERPC, the indeterminate localization of stenosis was in the distal part of the ductus choledochus in 24.7%, proximal stenosis in 27.4%, in the area of liver confluence / hilus - 46.6% and intrahepatic in 1.4%. In all patients, cholangioscopy with biopsy material sampling at 75.3% led to the identification of the cause - malignant and benign stenoses, concretions, Mirizzi's syndrome, echinococcal membrane obstruction, compression. Patients are referred to groups for surgical treatment, follow-up and curative cholangioscopy. The complications observed in this group were 8.14%, not requiring emergency surgery or emergency treatment. The diagnostic accuracy of the cholangoscopically navigated biopsy is 86.79%, with a sensitivity of 95.00% and a specificity of 87.1%.

In Group III, 'missed concretions', 38 patients underwent EChS as a control verification method after navigation treatment of choledocholithiasis or unclear cholangiogram at the end of the procedure. Predictors of this pathology were

noted the presence of duodenal diverticula, B-II gastric resection, the presence of a stricture distal to the concrement, undiscovered concretions in control fluoroscopy. No statistically significant correlation was found between the detected cholangoscopic "missed" concretions and the presence of altered duodenal anatomy, distal structure, and fluoroscopic diameter d. choledochus. No complications with zero lethality were observed.

In group IV 'Other', 42 patients were enrolled and ChHS was performed in 35 patients and PS in 7 patients. Indications for ChPS were proximal migration of biliary stent - 10, biliary stricture after failure of cannulation in four, biliary complications after liver transplantation - in 9 patients. All ChS performed were followed by follow-up treatment procedures - extraction of migrated prostheses, stenting, transpapillary drainage referral for surgical treatment. No complications associated with the manipulation were observed.

Dr. Karagyzov's study of the diagnostic and therapeutic capabilities of ChPS with the SpyGlass DS platform, conducted in a 186-patient series, confirms the high efficacy and safety and its benefits mainly in the diagnosis of indeterminate biliary strictures and the endoscopic treatment of so-called "difficult 'concretions in the biliary tract. The methodology is highly sensitive (over 75%) and 100% specific. Complications from the procedure were observed in 9.1%, which is commensurate with the reported complications of ERCP without ChPS. The most important treatment procedure through ChPS is the extraction of 'difficult' biliary concretions achieved in 90.9% of cases - a similar result compared to the publications of foreign authors in the literature review.

As predictors of unsuccessful extraction, the author cites concretions of size ≥ 25 mm, history of previous ERCP procedures, and duration of the procedure longer than 60 min. The biggest advantage of ChPS is the ability to directly visualize and take a targeted biopsy. The cholangiographic image has a sensitivity of 95% and a specificity of 87.1%, when working with SpyGlass - II generation, and of the navigated biopsy - 79.4% and 100%. The ChPS found missed calculi in classical cholangiography in 26.3% of cases.

ChPS is the solution of diagnostic and therapeutic behavior in a number of rare indications - extraction of proximal migrated stents selective cannulation of complex strictures, evaluation of cysts of intrahepatic and extrahepatic biliary tract, diagnosis of unspecified hemobilia, iatrogenic lesions of the biliary pathways, biliary complication after orthotopic liver transplantation, transpapillary drainage of the gallbladder after acute cholecystitis, and contraindications for surgery.

Per-oral panreatoscopy, despite the small number of cases in the study, has proven to be a highly effective procedure for unclear d strictures. pancreaticus, pre-operative staging of pancreatic tumors, lithotripsy of concrements in d. pancreaticus. No statistical processing was performed due to the insufficient number of cases in the individual subgroups.

In all groups, the author has provided descriptions of demonstrative cases, richly illustrated and presenting the efficacy of ChPS in individual patient populations.

Complications were observed in 9.1% of cases, manifested clinically as acute pancreatitis after ChPS, acute cholecystitis, hemobilia, acute cholangitis, acute bleeding from Papilla Vateri, perforation of d. choledochus, which are comparable to conventional ERPC procedures. None of the patients required emergency surgery or transfer to a resuscitation and intensive care unit with zero lethality.

A concentrated expression of the results obtained are the 17 conclusions and recommendations that were broadly presented in the review. They summarize the characteristics, indications, contraindications, behavior in established pathology, efficacy and safety of diagnostic and therapeutic ChPS.

The author has presented the expected 10 contributions of scientific, practical, original and confirmatory nature. The contributions are directly related to the introduction for the first time in Bulgaria of a high-tech methodology with a relatively safe profile, rich opportunities and potential in the diagnosis and treatment of diseases of the bio-pancreatic system.

In conclusion, the doctoral dissertation is an accurate and timely analysis of the place and capabilities of ChPS in the modern diagnostic-therapeutic algorithm applied to biopancreatic diseases. It proves that ChPS can be successfully and safely added to standard endoscopic ERCP and significantly improve outcomes in case of difficult biliary and pancreatic concretions and improve diagnostic accuracy in undetermined biliary strictures. ChPS has made significant progress in recent years, becoming a complex and risky procedure requiring two operators to intervene beyond conventional ERCP, easily and quickly by an endoscopist. The use of high resolution and new technologies can improve diagnostic capabilities and lead to routine application of the methodology, especially in high-risk patients. Facilitating the procedure and reducing costs would lead to widespread use of ChPS and the associated behavioral change in a number of biliary and pancreatic diseases.

Unsuitable grammatical expressions are used in the doctoral dissertation, the presentation of the results is cluttered with numbers, its retrospective design is not optimal for these studies, the volume of the literature review occupies almost 1/3 of the presentation, there is no direct comparison of the cholangoscopic treatment methods with the conventional ones in cases of "difficult" concretions in the biliary tract. No cost-effectiveness and real cost assessment was carried out. These remarks do not diminish the value of the doctoral dissertation.

Given the well-chosen pioneering topic of the doctoral dissertation for Bulgaria, the corresponding goals and tasks, the rich literary reference, the well-processed and illustrated reliable statistical processing, the practical conclusions drawn, and the doctoral student's own contributions, I suggest the Honorable Jury to vote with "Yes" the degree of Doctor of Medicine by Dr. Petko Ivanov Karagiozov.

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