**REVIEW**

**by Prof. Dr. Georgi Todorov, PhD**

**Head of Endocrine Surgery Clinic of USBALE "Academic Iv. Penchev"**

**of a dissertation for awarding the educational and scientific degree 'PhD'**

**Field of higher education 7. Health care and sports, Direction 7.1. Medicine**

**Scientific specialty "General Surgery"**

**Author: Dr. Anastasia Siemon Petresca**

**Form of doctoral studies: independent preparation**

**Institution: ASK UMBAL "Tokuda", Sofia**

**Topic: "Resectability of pancreatic head carcinoma - pre- and intraoperative criteria"**

**Scientific supervisor: Prof. Dr. Kiril Dragatnov, Ph.D., ASK UMBAL "Tokuda", Sofia**

**1. General presentation of the procedure and the doctoral student**

The set of materials presented by the doctoral student in paper and electronic media is in full compliance with the requirements of the current regulatory framework in the country, namely - Art. 74, paragraph 1, item 1 of the LHE, art. 24, para. 2, para. 3, para. 6 of the Regulations for the Implementation of the Law on the Development of the Academic Staff in the Republic of Bulgaria (PP ZRASRB) and art. 23, para. 6 of the Regulations for the Development of the Academic Staff in Acibadem City Clinic UMBAL "Tokuda" , Sofia.

The specified set of materials includes the following documents:

- Application to the Director of "Acibadem City Clinic UMBAL Tokuda", Sofia for disclosure of the procedure for the defense of a dissertation work;

– curriculum vitae in European format with the doctoral student's signature;

– a notarized copy of a higher education diploma;

– orders for enrollment in doctoral studies and for deduction with the right of defense;

– an order for conducting an exam from the individual plan and a corresponding protocol for passing the doctoral minimum in the specialty;

- appointment order and protocol of the meeting of an extended scientific collegium for preliminary discussion of the dissertation work and the decisions taken for the disclosure of the procedure and for the composition of a scientific jury;

– dissertation work;

- abstract for the dissertation work;

– a list of scientific publications on the subject of the dissertation;

- copies of scientific publications on the topic of the dissertation;

- declaration of originality and authenticity of the attached documents;

Dr. Anastasia Petresca has attached 8 (eight) full-text publications related to the topic of the dissertation work.

**Notes and comments on the documents**

The procedure for the defense of the dissertation, as well as the related documents, fully meet the requirements of the current regulatory framework in the Republic of Bulgaria. At the first absent meeting of the scientific jury, I was designated as a reviewer.

**Brief biographical data**

Dr. Anastasia Simeon Petresca graduated in medicine at the Faculty of Medicine of the Sofia University in 2001. In the period 2002-2007, she was a resident the Clinic for Surgical Diseases "Prof. A. Stanishev", UMBAL "Alexandrovska". She acquired a specialty in "General Surgery" in 2008. In the same year, she became part of the team of the Clinic for Liver, Biliary, Pancreatic and General Surgery, Tokuda Hospital Sofia Medical Center (now Acibadem City Clinic UMBAL Tokuda).

The doctoral student's desire for constant professional improvement and development is evidenced by the specializations and courses held - laparoscopic surgery, hepatobiliary surgery, pancreatic surgery (all at the Sofia University). There are also two specializations at Fundeni Hospital, Bucharest under the supervision of Prof. Irinel Popescu (years 2015, 2016), as well as a course at the Johnson and Johnson Institute, Cincinnati, USA on the use of automatic sewing machines.

On 19.04.2018, Dr. Anastasia Petresca was enrolled as a doctoral student of independent training in the scientific specialty "General Surgery" (order No. 161/19.04.2018) of the Executive Director of "Acibadem City Clinic MBAL Tokuda"). After successfully passing the doctoral minimum exam (06.10.2021) and internal defense (27.06.2022) she was dismissed with the right to defense (order No. 15-05-138/30.09.2022 of the Executive Director of "Ajibadem City Clinic UMBAL Tokuda).

**2. Relevance of the topic**

The topic of the dissertation work is extremely relevant for Bulgarian medicine both in a purely scientific and in a scientific-applied aspect for a number of reasons.

Pancreatic cancer is one of the most thanatogenic tumors. This is due to its aggressive biology: tendency to infiltrate neighboring tissues and structures; perineural, lymphovascular and vascular invasion; early lymphogenous and hematogenous dissemination; high rate of local recurrence and metachronous metastases after potentially "radical" resection. Especially with regard to surgical treatment of carcinoma of the head of the pancreas (PHC), there has been a substantial improvement in early outcomes (mortality and morbidity), but not in long-term outcomes—disease-free survival and overall survival. Late diagnosis remains a problem, as only 20% of cases are currently resectable. Local advancement with vascular infiltration is found in 40%, and in the remaining 40% - hematogenous and/or peritoneal metastases.

It is a serious challenge for the surgeon to decide preoperatively whether the particular tumor is resectable or not. There still remains a large proportion of cases judged preoperatively as radically operable, which was not confirmed intraoperatively.

Currently, generally accepted prognostic factors for resectability are lacking. Data from the literature are controversial, even contradictory. Some studies have found a dependence of resectability on certain factors, but many studies reject them.

The team of Acibadem City Clinic UMBAL Tokuda has accumulated over 15 years of experience in pancreatic resection surgery. This is a solid foundation on which Dr. Petresca stands and the main motivation for starting the study. Additional support in this type of study and in this particular case is the strong interventional gastroenterology at the doctoral student's institution. I admire the idea that the achieved results, formulated conclusions and recommendations will help in the daily work of other centers diagnosing and treating this pathology.

**3. Knowing the problem**

The literature review is presented in a volume of 32 pages (from page 6 to page 37 inclusive). The doctoral student has thoroughly examined all the modern information concerning PHC- epidemiology, frequency, risk factors, genetic aspects of carcinogenesis, clinical manifestations, diagnosis, treatment.

The description of the various diagnostic methods, their specificity, sensitivity and reliability in relation to resectability, as well as the surgical aspects to achieve radicality – total mesopancreatic excision, adequate lymphatic dissection, achieving R0, etc., occupy a central place in the overview.

All this proves the deep and detailed knowledge of Dr. Petresca on the topic of the dissertation work.

The review of the specialized literature ends with a short but very important conclusion (pp. 36-37). In it, the doctoral student formulates 7 conclusions on controversial and debatable issues concerning the diagnosis and preoperative assessment regarding the operability of the PHC. They are the main motivation for starting and conducting the study.

**4. Research methodology**

The purpose of the study is clearly formulated:

to analyze the reliability, sensitivity and specificity of some preoperative clinical, laboratory and instrumental data as predictors of resectability in PHC.

In line with it, and as it should be in any modern research, a working hypothesis was also built, according to which such predictors exist and their correct complex interpretation can be a reliable tool in assessing whether a KGP is resectable or not.

To achieve the goal and prove/reject the hypothesis, Dr. Anastasia Petresca formulates 5 tasks

1. Review of the medical documentation of the patients operated on the occasion of KGP in the "Clinic of Liver, Biliary, Pancreatic and General Surgery", ASK MBAL Tokuda for the period 01.01.2007- 31.12.2019 and selection of suitable cases for inclusion in the study ;

2. Analysis of some preoperative data, the resectability data and the patho-histological results of the resected specimens;

5. Development of an algorithm based on the preoperative data in a qualitative (presence or absence) and quantitative aspect (degree of manifestation) to refine the assessment of potential resectability in patients with KGP.

 One of them has 4 sub-points – concrete, precise and clear, without going into unnecessary details on the one hand, and on the other hand allowing for an in-depth scientific study.

I give a high rating to the formulated inclusion and exclusion criteria, on the basis of which a series of 400 cases was selected from among 695 patients, judged to be suitable for the purpose and tasks of the study.

The methods used are summarized in 7 groups, described in detail and well illustrated with intraoperative photographs.

Another proof of the doctoral student's research qualities is the division of the clinical material into three groups depending on the preoperative assessment and the volume of the intervention performed - radical, palliative and exploratory surgery. Of particular interest are the second group ('palliative') and the third ('exploratory') in which preoperatively they were considered suitable for radical surgery but intraoperatively this was rejected. In the further exposition, the doctoral student seeks an answer to the questions of what caused this "wrong" judgment and whether it could not have been "wrong".

**5. Characterization and evaluation of the dissertation work and contributions**

The dissertation has a volume of 144 standard stations. Illustrated with 38 tables and 15 figures. The bibliography includes 199 sources. The review regarding the literature review, purpose and objectives was stated above. Here I will focus on the achieved results, their presentation and discussion, conclusions and contributions.

"Own Results" (pp.50-78) and "Own Results Analysis and Discussion" (pp.79-108) represent the most extensive chapters in the dissertation.

The analysis of own results is clear and analytical. A good impression is made by the comments at the end of each subsection, which clearly summarize and emphasize the important information.

Important from a scientific and from a practical point of view are a number of established dependencies of the resectability of PHC as well as rejection of other such. All this is based on thorough statistical processing and is well argued and presented descriptively, in tabular and graphical form.

On page 113, Dr. Anastasia Petresca formulates 13 conclusions, which are based on the overall analysis of the obtained results and are a logical conclusion of the dissertation work. Some of them are confirmatory, others original, such as conclusions 3, 12 and 13, e.g.

ERCP with EPH stenting in patients with PHC and mechanical jaundice has no prognostic value in terms of resectability, but it is an important and irrevocable tool in the preoperative preparation of this contingent of patients for possible future radical intervention. As well as conclusion 13: In patients with BR-PDAC, it is appropriate to use the full range of preoperative diagnostic methods, as well as consultations with relevant specialists and assessment of each individual patient according to the "ABC"-methodology.

4. Most of them are of a confirmatory nature, and those with numbers 4 and 5 are of an originally applied nature. I accept and acknowledge all contributions made by the dissertation.

**6. Evaluation of the publications and personal contribution of the doctoral student**

Dr. Anastasia Petresca presents a list of eight publications related to the topic of the dissertation, all eight of which are full-text articles or full-text reports printed in proceedings of national scientific forums. I would like to point out that in the bibliography of the dissertation work, not a single Bulgarian author is cited. This in no way reduces the value of the work, but I believe that the inclusion and discussion of our experience would only contribute to its completeness and give room for discussion of native experience in this pathology.

After a detailed review of the dissertation work and the publications related to it, I give an extremely high assessment of the overall work of Dr. Anastasia Petresca on the prediction of the resectability of PHC.

A dissertation is an in-depth study. The work on it, the obtained results, their analysis, the conclusions drawn and the contributions prove the personal merits of the doctoral student.

**7. Abstract**

The abstract to the dissertation work of Dr. Anastasia Petresca meets the requirements in terms of volume and content and gives a sufficiently clear idea of ​​the essence of the development, reflects in sufficient detail the results achieved and the formulated conclusions.

**CONCLUSION**

The dissertation work of Dr. Anastasia Simeon Petresca on "Resectability of carcinoma of the pancreatic head - pre- and intraoperative criteria" contains scientific and scientific-applied achievements, which represent an original contribution to science and meet all the requirements of the ŽARSRB, the Regulations for implementation of the ZRASRB and the Rules of the ACK UMBAL Tokuda. The presented materials and dissertation results fully correspond to the specific requirements, are original in nature and no plagiarism is detected.

The dissertation shows that the doctoral student has in-depth theoretical knowledge, demonstrating qualities and skills for independent conduct of scientific research.

It is important for me to note and emphasize that I know the dissertation from the first steps in the field of surgery. During his professional career, Dr. Petresca is distinguished by her ambition, desire to improve and his desire to master and implement the innovations in our specialty. All this combined with high professionalism and undoubted personal qualities make her one of the leading surgeons in the clinic.

In conclusion, I confidently give my positive assessment of the dissertation work presented to us and propose to the esteemed scientific jury to award the fully deserved educational and scientific degree "PhD" to Dr. Anastasia Simeon Petresca in the doctoral program in "General Surgery", for which I strongly vote yes

Prepared the review:

Date 07.11.22 (Prof. Dr. Georgi Todorov, PhD)