

**ВОЕННОМЕДИЦИНСКА
АКАДЕМИЯ**

София 1606, бул. "Г. Софийски" №3,
Република България
Тел.: (+359 2) 92 25 188, 92 25 238



**MILITARY MEDICAL
ACADEMY (MMA)**

3, G. Sofiyski Str., 1606 Sofia,
Bulgaria
Tel.: (+359 2) 92 25 188, 92 25 238

To the Head of Scientific Jury,
appointed by Order No. 15-05-148 / October 18, 2022
of the Executive Director and Prosecutor of
„Acibadem City Clinic General Hospital for Active Treatment (GHAT) Tokuda“ EAD

REVIEW

by Assoc. Prof. Dr. Tsonka Lukanova, M.D.

First Clinic of Abdominal Surgery, GHAT – Sofia at MMA

Department of Surgery, GHAT – Sofia at MMA

Concerning: Defense of a dissertation paper for acquiring the educational and academic degree 'doctor' in the field of higher education 7. Health Care and Sport, direction 7.1. Medicine, doctor's program 'General Surgery', on subject: 'Resectability of Carcinoma of the Head of Pancreas – Pre- and Intraoperative Criteria'; worked up by Dr. Anastazia Simeon Petreska, a graduate student of self-training at the Clinic of Liver, Biliary, Pancreatic, and General Surgery at 'Acibadem City Clinic GHAT Tokuda' EAD, with Prof. Dr. Kiril Draganov, D. M. Sc., as a supervisor.

The materials – as paper and electronic copies - presented to me, correspond to the procedures for acquiring of educational and academic degree 'doctor' at 'Acibadem City Clinic GHAT Tokuda' EAD according to the statutory requirements and published normative documents for this purpose.

Dr. Anastazia Simeon Petreska graduated her higher education in medicine at the Medical University – Sofia in 2001, and acquired specialty of 'general surgery' in 2008 after

implemented specialization at the Clinic of Surgical Diseases 'Prof. Dr. Alexander Stanishev' – Second Clinic of Surgery, at University General Hospital for Active Treatment (UGHAT) 'Alexandrovska'. She is a member of the medical team of Clinic of Liver, Biliary, Pancreatic, and General Surgery, Acibadem City Clinic UGHAT Tokuda from 2008 till present, and is a part-time assistant at the Medical Faculty of Sofia University 'Sv. Kliment Ohridski'.

The scientific work 'Resectability of Carcinoma of the Head of Pancreas – Pre- and Intraoperative Criteria' presented for assessment, has been worked up in correspondence with the requirements of acquisition of academic and educational degree 'doctor', and illustrated with 15 figures and 38 tables; it has a total volume of 144 standard pages, distributed in the following way:

1. Introduction – two pages
2. Literature review – 29 pages
3. Conclusion of the literature review – two pages
4. Methods of the study: purpose and tasks – two pages
5. Methods of the study: material and methods – nine pages
6. Personal results – 29 pages
7. Analysis of the personal results and consideration – 29 pages
8. Conclusion – two pages
9. Final statements – three pages
10. Contributions – one page
11. List with publications, related with the dissertation paper – two pages
12. Reference – 25 pages

The dissertation paper discusses current – for the specialized community – subjects, related with resectional pancreatic surgery, namely the determination of resectability of carcinoma of head of pancreas, which turns out to be one of the critical steps in the therapy of patients with localized disease. The emphases are set on the improved preoperative diagnostics, mainly the interventional methods, operative techniques and equipment, the quality of intensive cares, introduction of neoadjuvant chemotherapy, as well as all listed

factors, which – as a complex – lead to improved postoperative results, namely mortality and morbidity in patients with such a pathology. The author, however, noted – against this background – that although the absolute number and relative ratio of cases with carcinoma of head of pancreas progressively decreases, the ones assessed preoperatively as resectable, but with intraoperatively proved nonresectability, stay embarrassingly high; and searching for an answer of the reasons for that follows in the next work.

The presented on 29 pages literature review is comprehensive, clearly structured, and of current interest. The general characteristics of the carcinoma of pancreas (CP) and, in particular, of carcinoma of head of pancreas (CHP), are expressed in concrete form in the first chapter – demographic data, carcinogenesis, risk factors, clinical picture. In the second chapter of the review are discussed surgical and oncological aspects, while the questions related with the total mesopancreatic excision (TME), the prognostic role of paraaortic lymphonodular state, etc., are considered in details. The prognostic factors for resectability - a main subject of the dissertation paper – are comprehensively presented in the following third chapter, while the emphasis is set on the classical imaging methods (ultrasonographic examination, MRI, CAT), and, in particular, the computed tomography examination with intravenous contrast with a view to determination of involvement of the main blood vessels – superior mesenteric vein, portal vein, superior mesenteric artery, common hepatic artery, and celiac trunk, in the context of the subjects worked up, followed logically by thoroughly discussed adopted definitions of current interest for the resectability of CP. The more specific interventional methods for diagnostics present particular interest in the review; they are transferred subsequently to the overall working up as well, among others – endoscopic retrograde cholangiopancreatography (ERCPG) with possibilities of therapeutic effect (and the indications for that), as well as of the innovative, highly specialized methods as endoscopic ultrasonography with its role for determination of resectability of CHP, the high sensitivity and specificity of endoscopically navigated fine-needle biopsy, as well as the direct oral cholangiopancreatography, the role of which in the staging and preoperative assessment of pancreato-biliary neoplasms is still an object of studies; the specific at this time indications for pancreatoscopy are, however, given.

The literature review ends with seven well-grounded final statements, a part of which are of particular current interest in the context of the indications for the operative treatment,

referral of patients with icterus to highly specialized medical centers with a view to therapeutic interventional procedures and reduction of the percentage of explorative laparotomies and palliative interventions in non-resectable cases.

The set aim – ‘Analysis of the Reliability, Sensitivity, and Specificity of Some Preoperative Clinical, Laboratory, and Instrumental Data as Predictors for Resectability in CHP (pancreatic carcinoma)’ – is clearly formulated with a subsequent, directly following from it, work hypothesis and five concrete tasks.

Already in the beginning of the chapter ‘Material and Methods’, one is impressed with the exceptionally precise formulation of the design of study, which indicates confident handling with the scientific semantics in the context of processing of imposing subsequent clinical material. After undergoing of strict selection of 695 patients who were operated at this Clinic due to CHP, in the period from January 2007 to December 2019, 400 patients were selected for the purpose of this dissertation paper.

The used clinical, laboratory, medical imaging, interventional diagnostic and therapeutic, surgical (interventions of various character and dimensions), parahistological and statistical methods were described in details in seven groups.

In the following third chapter, named ‘Personal Results’, data were systematically presented about the type and volume of the performed intervention (63.3% radical intervention with achievement of R0), subdivision according to the preoperative assessment and intraoperative finding, while the criteria ‘resectability’ was in the basis of further analyses and searching of statistically reliable dependencies of the rest parameters – demographic data, as well as data from the different groups of methods. An impression is made – already in the beginning – by the occurrence of ‘one of the unsolved problems’ in the present-day pancreatic resectional surgery (or at least for Bulgaria) – *‘in 31.9% of the cases $n = 124$ was planned radical surgery, which in practice was not realized after the found non-resectability with the exploration. In other words the information for absence of vascular invasion and/or organ and/or peritoneal dissemination of medical imaging turned out to be false positive’.*

Concrete results for the demographic distribution and clinical data follow, with subsequent assessment of the value of CA 19-9 – its average value was considerably lower in operable cases compared to non-operable ones, without finding of statistical reliability ($p =$

0.053); a borderline prognostic value of 500U/ml was suggested, the significance of which must not be interpreted by itself, but only in combination with other factors. Interesting results were presented regarding the values of bilirubin, and the percentage of 38% of radical surgeries, performed in persisting icterus after ERCPG. There were subsequent results about the searched in practice answers by the surgeon in the context of multidisciplinary approach for diagnostics and treatment of patients with CHP – size of tumor and main pancreatic duct, assessment of the vascular and liver state, reliability of the histological diagnosis (in this case mainly EUS-FNA). A concrete practical result is that the risk of 'large' tumor (> 35mm) – turning out to be nonresectable – is 159.7 higher, than in 'small' tumor (< 20mm). Regarding the infiltration of blood vessels, found by summarized data from CAT and MRI on one hand, and intraoperative and pathohistological data on the other hand, both non-invasive methods demonstrated comparatively good sensitivity and specificity, respectively 80.3% (n = 176/219) and 77.1% (n = 64/83). The infiltration of main venous blood vessels, found by the methods of ultrasonographic-endoscopy, demonstrated statistically reliable informativeness and correlation with the resectability. The statistical working up of information concerning of ERCPG and stenting of extrahepatic bile ducts did not find dependence between the procedure on one hand, and resectability of the tumor on the other hand.

In the chapter 'Analysis of the Personal Results and Consideration' consistently and systematically were analyzed the results, related with the response of the set in the beginning of five concrete tasks. The comments after every thorough comparative consideration with the present data in the world literature summarize and make concrete final statements for the respective index. One is impressed by the elements of the author being critical of herself and formulation of a series of well-grounded recommendations with the purpose of improvement of preoperative assessment in patients and reduction of the percentage of explorative and palliative interventions. The borderline resectable CHP and introduction in Bulgarian practice of ABC-methods were stressed, with assessment of conditional state of patient by means of Surgical Outcomes Analysis and Research (SOAR) Pancreatectomy Score. The prognostic factors for resectability of CHP were systematically analyzed – data from medical histories and physical findings, tumor markers, the persisting icterus, and waiting in the course of time; the comment is important that the data of all medical imaging examinations have to be followed as 'parts of

a puzzle' in order to be reviewed together, and the overall information to be juxtaposed, so that none of them shall have absolute reliability, sensitivity, and specificity – in the personal results CAT and MRI demonstrated comparatively good sensitivity and specificity (the already cited 80.3% and 77.1%) for the presence or absence of infiltration of main blood vessels by CHP; the endoscopic ultrasonography is accepted as exceptionally useful and sufficiently informative regarding the dilatation of the main pancreatic duct and determination of the vascular infiltration. The insufficient reliability of EUS-FNA – as the author noted – could be considered in a subsequent multidisciplinary prospective study. The applied in the Clinical Center criteria for stenting of extrahepatic bile ducts were clearly indicated. There followed a precise analysis of the surgical technique and methods with an accent on the total mesopancreatic excision (TME), pathological examination of the resection margins, and definition of standard lymph dissection. A logical final statement in the conclusion of chapter 'Analysis of Personal Results and Consideration' is that 'pancreatic oncological surgery has to be practiced in Bulgaria only in medical centers offering the complete set of diagnostic means, inclusively interventional ones, having major experience in the resectional surgery of pancreatic gland, and with present structures for medicinal treatment and radiotherapy, with the purpose of a complex approach in every concrete patient'.

Based on the obtained results and their consideration, 13 final statements were formulated. The final statements themselves are clear, and correspond to the indicated tasks, and also summarize the signification of the scientific work with an accent on the resectability of CHP.

The 5 contributions of the graduate student were specified, while subdivision in one of them was reported. The listed contributions may be subdivided to such with original (1; 3.2; 4), scientific and theoretical (2; 3.1), and scientific and practical (5) character. The final statement 3.2, which describes the bringing out of prognostic factors of resectability based on personal material, is exceptionally important and may categorically defend a personal position.

A list of 8 publications is attached, which cover the overall subjects of the dissertation paper and disclose the systematical entity, as well as the successiveness in publication of the results in the course of time and deepening of the analysis with accumulation of experience.

The reference information is a thorough and present-day one – it contains 199 titles in Roman alphabet, cited in classical AMA format.

The dissertation paper contains scientific, scientific and applicable, and applicable results, which represent an original contribution in science and correspond to all requirements of the Law for Development of the Academic Staff in the Republic of Bulgaria (LDASRP), the Regulation for Application of LDASRB, and the respective Regulation for Development of the Academic Staff of 'Acibadem City Clinic UGHAT Tokuda' EAD.

With a view to all of the above mentioned, as well as the personally known to me research and professional qualities of the graduate student Dr. Anastazia Petreska, I express my explicit positive statement regarding the defense of the dissertation paper 'Resectability of Carcinoma of Head of Pancreas – Pre- and intraoperative Criteria' and delegate my complete support for conferment of educational and academic degree 'doctor'.

November 7, 2022

Sofia, city

Member of the Jury:

(Assoc. Prof. Dr. Tsonka Lukanova, M.D.)

