

**UNIVERSITY OF MEDICINE AND PHARMACY
„CAROL DAVILA” BUCHAREST
DOCTORAL SCHOOL
THE FIELD: MEDICINE**

**DIGESTIVE ONCOLOGICAL SURGERY IN THE
AGE OF PERSONALIZED THERAPY**

ABSTRACT OF ABILITATION THESIS

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The paper "Digestive oncological surgery in the age of personalized therapy" has five chapters.

Chapter 1 is a summary of my professional career, presenting a series of milestones in medical, didactic and research activity. In short, I have been a senior physician in General Surgery since 2009 (MoH Order 1200/2009), I have gone through all academic ranks starting with junior assistant in 2002 (Rector of University of Medicine and Pharmacy "Carol Davila" Bucharest - UMPCDB Decision 12856/1.10.2002) and ending with associate professor in 2023 (Rector of UMPCDB Decision 3422/28.09.2023), I have defended my doctoral thesis "*Liver metastases of colorectal cancer – diagnosis and treatment*" (under the coordination of Professor Irinel Popescu) in December 2009 (with the PhD/MD title according to MoEd Order 3492/23.03.2010), and between 2010 and 2013 I have followed a postdoctoral programme in a project coordinated by UMPCDB ("Supporting postdoctoral research in the field of reconstructive transplant surgery – POSTDOC-TRANSPLANT").

In chapter 2 I present my medical activity, highlighting the main surgical areas that I have focused on and my main results. Between 2002 and 2023 I have worked in the "Dan Setlacec" Center for General Surgery and Liver Transplantation from the Fundeni Clinical Institute, dedicated to digestive oncological pathology, including hepato-pancreato-biliary (HPB), focusing on developing surgical knowledge and skills on these topics. In 2010, I have earned the certificate of complementary studies in Liver Surgery and Liver Transplantation (C Series no. 025628), and in 2012 the certificate in Oncological Surgery (C Series no. 029535). I have also attended a series of interuniversity courses and preceptorship programs in onco-surgical strategies addressed to hepato-bilio-pancreatic malignancies and liver metastases of colorectal origin (at Paul Brousse Hospital in Paris), as well as an observership programme in liver transplantation at the Department of Liver Transplantation and Hepatobiliary Surgery in the Asan Medical Center Seoul (the center with the highest annual volume worldwide of liver transplants from living donors). As a result, in over 15 years I have performed more than 50 curative-intent interventions each year for colorectal and gastric cancers, and in the last 7 years I have performed annually over 25 liver resections mainly for primary or secondary liver malignancies. Starting November 2023, I activate at the 2nd Surgery Clinic in the University Emergency Hospital Bucharest (UEHB), and in the last 3 months I have performed 7 liver resections, 9 colorectal resections, 2 radical gastrectomies and 4 multivisceral resections for genital or colorectal cancers with peritoneal metastases. Concerning the contributions to the development of HPB surgical procedures, I was part of the surgical team that successfully performed in 2016 the first ALPPS procedure

in Romania (and the main author of the article that reported this first case). In 2023 I performed for the first time in Romania, together with a team of surgeons from Fundeni C.I., liver venous deprivation (LVD) for conversion to resectability in a patient with initially unresectable colorectal liver metastases. Furthermore, in the case of the treatment of patients with acute pancreatitis requiring a pancreaticoduodenectomy for a concomitant malignancy, my personal contribution's novelty and importance were confirmed by being published in *Hepatobiliary & Pancreatic Disease International*, IF = 3.7 at that time (Hepatobiliary Pancrea Dis Int. 2020 Feb; 19(1):94-96: Deliberate external pancreatic fistula after pancreaticoduodenectomy performed in the setting of acute pancreatitis and its internalization through fistula-jejunostomy).

In chapter 3 there is my teaching activity since 2002, supervising both students and residents. Starting with 2016, when I became lecturer, I have held courses for students in the fourth and fifth years of study, including series in English. These courses have always had clear educational objectives, achieved by presenting alongside the theoretical notions a series of clinical cases, as well as suggestive case images, and they ended with a series of tests to assess their efficiency. In over 21 years of academic career, I have authored or co-authored 13 chapters published in the Surgery manuals/courses addressed to UMPCDB students (10 in Romanian and 3 in English). I have also tried to stimulate students' interest in a series of extracurricular topics in the field of General Surgery by lecturing in various editions of the UMPCDB Congress (2021, 2022, 2023), as well as in a series of student congresses, and in the last 6 years I have supervised the Bachelor of Medicine thesis for 7 of my students.

In addition, since 2017, I have developed and presented annually the course in Liver Pathology, in accordance with the training curriculum for first-year General Surgery residents, developed by Department 10 Surgery of UMPCDB. Also, for the first edition of *Surgery Manual for residents* (published in 2021 under the coordination of Professors Traian Pătrașcu and Mircea Beuran, ISBN 978-606-011-164-1) I have authored the "Liver pathology" chapter. Finally, I would like to emphasize the gradual involvement in the research work of all my residents, and in the last 10 years every one of them has contributed to the elaboration of at least one published article.

On the continuous medical education: I was a trainer in two educational projects, I have held lectures in various postgraduate/pre-congress courses and I have co-authored 13 chapters in various treatises or textbooks (including an international one).

In chapter 4 I have the scientific and research work: main author of 26 articles (12 in ISI journals with IF, 6 in ISI journals without IF and 8 in journals indexed in international

databases - IDB) and co-author of 135 articles (119 in ISI journals with IF, 9 in ISI journals without IF and 7 in IDB journals), with a cumulative main author impact factor of 25,113.

In the main author articles, I have focused not only on clinical research, but also on fundamental research, assessing the impact of molecular factors on the prognosis of patients with various oncological diseases (e.g. the impact of RAS genes mutational status on the prognosis of patients with resected liver metastases of colorectal origin). Besides the above-mentioned article presenting a novel surgical approach in the treatment of patients with acute pancreatitis who require pancreaticoduodenectomy, another one paper was the first study published on the correlation between primary colorectal tumor location and the three subclasses of metastatic disease (M1a, M1b, and M1c), according to the latest edition of the cancer staging system published by the American Joint Committee on Cancer Staging. Also the article "Aggressive surgical approach in patients with adrenal-only metastases from hepatocellular carcinoma enables higher survival rates than standard systemic therapy" was the first study worldwide to compare the efficacy of adrenalectomy with that of sorafenib (standard treatment at that time) in patients with adrenal metastases of hepatocarcinoma. In several other articles, as main author I have refined the prognosis of patients with digestive malignancies (e.g. metastatic colorectal cancer), according to a series of clinical (number of metastases, location, percentage of metastatic lymph nodes) or therapeutic parameters (width of oncological safety margin, adjuvant chemotherapy), allowing not only the prognostic stratification of patients, but also the individualization of treatment and postoperative monitoring regimen.

By including the Surgery Centre from Fundeni C.I. in a working group on hepatobiliary pathology coordinated by Professor Timothy Pawlik from Ohio State University and collaborating with researchers from prestigious centres in Europe, Asia, Australia and the United States of America, I had the chance to test certain clinical hypotheses regarding the treatment of colorectal liver metastases on larger groups of patients and to conclude certain correlations between the molecular profile of these cancers and patients' prognosis. Within this multi-institutional collaboration, we have used new ways of data analysis (e.g. machine learning) in order to achieve a high accuracy analysis of a very large volume of data and to generate algorithms to be used in the prognostic stratification of patients. Moreover, this team has evaluated the therapeutic and prognostic implications of various clinical, bio-humoral, histopathological, and molecular features, in patients with liver tumours (intrahepatic cholangiocarcinoma, hepatocarcinoma, biliary cystic tumours, liver metastases), and the results allowed prognostic stratification of patients, creating the

base for the individualization of treatment according to the mentioned parameters. The results of these studies have been reported at numerous international scientific events and published in some of the most prestigious journals (including *JAMA Surgery*, *Annals of Surgery* and *Nature Genetics*).

In addition, I was a member of the research team in an international project and in 3 national projects.

Overall, the scientific impact of the papers developed with my involvement has reached 4,709 citations in 3,005 articles, according to Web of Science (Hirsch index = 36).

In Chapter 5 I have listed the main directions of development I focus on, some of the most important being as follows:

- To create a department or service of oncological and hepato-pancreato-biliary surgery in UEHB;
- To develop and implement new aggressive surgical techniques in patients with peritoneal metastases of digestive cancers;
- To contribute to the creation of a treatise on surgical techniques and a video atlas of surgical interventions including all procedures in the training curriculum in General Surgery (developed under the coordination of Department 10 Surgery, UMPCDB);
- To contribute to the creation of a national professional association for peritoneal malignancies surgery;
- To guide young doctors (residents) in developing research topics and, after the admission to a doctoral program, to coordinate them in the elaboration of their doctoral thesis;
- To guide graduates of doctoral studies in developing research projects (to further develop the knowledge already acquired) with which they may participate in competitions such as "Postdoctoral research projects" or "Research projects to stimulate young independent teams", coordinated by the UEFISCDI (Executive Agency for Higher Education, Research, Development and Innovation Funding);
- To develop at the UEHB a project on the "Identification of predictive biomarkers for the response to aggressive onco-surgical treatment of patients with metastatic peritoneal ovarian cancer", in order to participate in a future call launched by UEFISCDI Programme 1 "Development of the national research and development system", Subprogramme 1.2 "Institutional performance";

- To create a partnership project between UEHB and one of the international centers in the multi-institutional team, focused on the correlation of molecular markers with the therapeutic response in patients with hepatobiliary tumors, in order to personalize treatment and improve survival;
- To participate in the creation of a biobank at the UEHB that will enable translational research in oncology both in research projects at UEHB level and in (inter-)national projects with UEHB as partner. This will allow the inclusion of young MD/PhD students in research projects and will create the basis for a translational medicine center within UEHB.

The paper is accompanied by relevant iconography from our publications and by more than 120 bibliographic references.