Universitatea de Medicină şi Farmacie "Iuliu Haţieganu"
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Habilitation thesis

CONTRIBUTIONS TO THE DEVELOPMENT OF TRANSTHORACIC ULTRASONOGRAPHY AND TRANSLUMINAL UPPER DIGESTIVE DIAGNOSTIC METHODS

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SYNOPSIS

This habilitation thesis synthesizes my professional, scientific and academic achievements in the medical field, focusing on the personal contributions to the ultrasonography and ultrasound endoscopy for diagnosis and intervention, starting from the year 2012, when I deferred my doctoral thesis at the "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca.

The thesis is structured in three parts: the first part presents the course of my didactic career, including the professional, scientific and academic accomplishments in the ultrasonography and diagnosis and interventional ultrasound endoscopy, up to the present moment. The second part covers the scientific contributions through of the knowledge at the present moment in the fields of bone ultrasonography, transthoracic-mediastinal ultrasonography and echoendoscopic biopsies of focal hepatic lesions, followed by contributions of original research – own series of percutaneous bone biopsies guided by ultrasound, ultrasound endoscopic pulmonary biopsies, echoendoscopic liver biopsies, conducted in national premiere. The third part of the thesis presents future projects in the professional, research and academic domains.

From the professional point of view, I obtained the title of senior consultant with double specialty, Internal Medicine and Gastroenterology. At the present moment I work as a chief at the Gastroenterology Department and Diagnosis and Therapeutic Digestive Endoscopy Unit at the County Emergency Clinical Hospital Cluj Napoca, in the Medical Clinic I.

Throughout my training, I acquired multiple imaging techniques for diagnosis – some classical, such as the abdominal echography and digestive endoscopy, others less common– namely, thoracic echography and digestive echoendoscopy. In this way, I contributed to the development of thoracic ultrasonography – non-cardiac – in our country. In this field, I also conducted my doctoral research, covering the use of the bioptical percutaneous ultrasound guided methods in the thoracic pathology. Subsequently, I also contributed to the dissemination of the method and information through several postgraduate courses – addressed mainly to pulmonologists and internist physicians. I have thus brought my contribution to the development of thoracic

ultrasonography in Romania, by holding numerous presentations at the national conferences of the Society of Ultrasonography in Medicine and Biology (SRUMB), other conferences and as part of several projects of the European Respiratory Society and the National Pulmonology Society. In the field of pulmonary and mediastinal percutaneous biopsies with ultrasound guidance I acquired, probably, the largest case load at national level, continuing in this way the work I started during my doctoral thesis.

Other applications, which I developed as a first at national level, consist of the introduction of ultrasound guided percutaneous biopsy diagnostic methods for osteolytic lesions. The complex interventional echography preparation in atypical fields allowed me to develop the techniques of transesophageal pulmonary biopsies, then vertebral biopsies (in world premiere) and other types of biopsies unknown in the field of digestive echoendoscopy. Furthermore, I concluded the first cases in Romania of pelvic abscess drainage through echoendoscopic, transrectal abord.

As a recognition of the personal contributions to the development of the thoracic and interventional echography, I have since 2018 been elected as a member of the Directorial Committee of SRUMB. I am a member of the European Federation of the Societies of Ultrasonography in Medicine and Biology (EFSUMB) and the World Federation (WFUMB), as well as the European Society of Gastroenterology (ESGE).

From the didactic-academic point of view I became, through competition, teaching assistant in 1997, assistant professor in 2001, lecturer in 2013, respectively associate professor in 2018, within the Discipline Medical I – Internal medicine, cardiology and gastroenterology at the Faculty of Medicine of UMF "Iuliu Hatieganu" Cluj, integrated clinically in the County Emergency Clinical Hospital, Cluj-Napoca. I held practical stages and delivered lectures in Internal Medicine - Gastroenterology to the students from Vth year, then IVth year at the Faculty of General Medicine of UMF Cluj – the Romanian and French speaking lines of study. Since 2018 I have become a tenured professor of modules in internal medicine- gastroenterology, for both the Romanian and the French lines of study. I have proposed and held an optional course for students - *Notions of thoracic-abdominal echography and digestive echoendoscopy – an integrative approach*, since the academic year 2018-2019. I have also been a collaborator to postgraduate courses in General Ultrasonography, Obstetrical and Gynecological Ultrasonography, needed to acquire the attestation of complementary studies in

Thoracic Ultrasonography, as well as a course in The Basics of Interventional Ultrasonography, addressed to specialist physicians. Since 2017 I have become the coordinator and regional responsible for the courses of general ultrasonography needed to obtain the competence. Since 2019 I was assigned the role of regional coordinator for the preparation of resident physicians in gastroenterology.

I have contributed to the editing of university textbooks (collaborator/ co-author - 2) or postgraduate textbooks (co-author - 1).

I have been a member of the admission committee for doctoral studies at UMF Iuliu Haţieganu. I represented UMF Cluj in the quality of president or member of the Examination Board for Specialist or Senior physician in Internal Medicine and Gastroenterology, as well as academic promotion boards (assistant, lecturer, associate professor) in the university centre of Cluj-Napoca. Furthermore, I have been a member of the Examination Boards nominated by the Health Ministry, with regards to achieving competence in Ultrasonography in Obstetrics and Gynecology. In the past few years I also had a constant participation in the Written theses evaluation and Practical exam evaluation Commissions for the Bachelor's degree examinations.

My scientific activity includes the publication as author/co-author of 10 chapters in books/specialty courses, 3 chapters in national specialty treaties and 2 chapters in international specialty books. Out of these, 6 were published in the last promotion (the last 2 years). I published over 40 scientific articles in peer reviewed journals, indexed in international databases. Currently, the Hirsch index is 6 according to Web of Science, 7 according to Scopus and 8 according to Google Scholar, accumulating 250 citations in Google Scholar platform, respectively over 110 in Web of Science. Some of the articles were derived from the 6 research grants, for 2 of them being project manager / director, one won by international competition (EIT Health Innostars 2019 - Horizon 2020 platform). I am also part of the team of investigators in 7 international randomized clinical trials, in 5 having the status of principal investigator.

From the organizational point of view, I contributed as a member of the organizing committee, respectively the scientific committee of several national medical manifestations of ultrasonography and gastroenterology.

I have been a reviewer of a number of articles published in ISI indexed journals - Medical Ultrasonography, Medical Science Monitor, Experimental and Therapeutic Medicine, Arab Journal of Gastroenterology, American Journal of Case Reports, Case Reports in Gastrointestinal Diseases, etc.

In the first section of the second part of the thesis we have reviewed the scientific contributions through syntheses of the current state of knowledge in the field of ultrasonography - respectively, review type articles dedicated to ultrasound-guided bone lesions biopsies (*Ultrasound-guided bone lesions biopsies - a systematic review. Ultrasound 2017; 19 (3): 302-309)* and biopsies of liver focal lesions (*Diagnostic yield of endoscopic ultrasound-guided biopsy of focal liver lesions. Medicine and Pharmacy Reports 2019; 92 (1): 15-20*), performed in national and some international premieres. We have also included a pictorial article on the ultrasonographic evaluation of mediastinal masses (*Mediastinal masses - transthoracic ultrasonography aspects. Medicine 2017; Dec; 96 (49): e9082)*, also a premiere approach.

In the second section of the second part of the thesis I present the original research contributions, materialized in publications in journals indexed in international databases (ISI), in the field of ultrasonography. Thus, I will present the contributions in the fields of introduction into the arsenal of diagnostic procedures of percutaneous bone biopsies (*Ultrasound-guided biopsy of osteolytic metastasis - could be less than three colors enough? Med Ultrasound 2018; 20 (1): 50-56*), own series published in a national premiere, in which we obtained a very good diagnostic accuracy (over 90%), using a maximum of 2 bioptic passages.

The contributions regarding the original research in the field of interventional echoendoscopy will include two papers.

The first study evaluates the diagnostic contribution of echoendoscopy in central-paraesophageal lung tumors (*Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) of paraesophageal lung tumors - diagnostic yield and added value. Med Ultrasound 2019; 21 (4): 377-381*), still a premiere contribution of this kind at national level, in which we included 19 patients, managing to confirm the malignancy in all the included cases.

The second study presents a prospective analysis of the added value of echoendoscopy in the diagnosis of hepatic focal lesions - also a national premiere experience (*Accuracy of endoscopic ultrasound-guided biopsy of focal liver lesions. Med Ultrason 2020. doi*: *10.11152 / mu-2078*) in which we analyzed a set of 48 patients, obtaining a diagnosis rate of 98%, without complications.

The third part of the thesis included some of the directions for adademic, scientific and professional development, some of them representing the continuation of the described concerns, which I think will ensure a better visibility of my personal research and of our University at international level.

Thus, for the medical students, I proposed and created for the first time in the academic year 2018-2109, an optional course of *Notions of thoraco-abdominal ultrasound and digestive echoendoscopy - integrative approach*, to which we registered 100 students, that was voted to be held in the next and the following academic years and which I intend to further improve.

In the coming years I will propose to conduct workshops in the field of chest ultrasonography and digestive echoendoscopy with atypical indications, in order to popularize these less known and less used procedures, that have a special impact in the management of oncological patients and beyond.

With regards to postgraduate courses, I will try to improve the quality of the courses offered. In my new capacity of coordinator of the residents in gastroenterology, I will promote integrative training, with multidisciplinary notions offered to the young colleagues. I will apply the same principles to the other postgraduate courses to which I am a contributor. I will support younger colleagues in their professional and scientific development by co-opting them in research projects or clinical trials.

The main fields of research that I am targeting are:

- evaluation of the added value of echoendoscopy in the diagnosis of primary and secondary liver tumors, respectively the assessment of the contribution of transgastric / transduodenal hepatic aspirating puncture in these cases and the eventual repositioning of the EUS procedure in the diagnostic algorithm - doctoral study in course (Dr. Vlad Ichim);

- evaluation of genomic changes and status of PD-1 / PD-L1 in pancreatic adenocarcinoma, by an echoendoscopic puncture, in order to achieve a prognostic predictive score, with a doctoral study in this respect (drd. Adrian Mucilean) in which I am collaborating;
- possibilities to increase the performance of diagnostic and interventional transthoracic and transesophageal ultrasonography (including with contrast medium) in the pathology of the chest wall, pleura, lung and mediastinum (ongoing and submitted research projects of PED type, respectively, letter of intent in the application to Horizon Europe 2021);
- development of bone ultrasonography - diagnostic and intervention (echo bone biopsy) and of the area of international priority that I developed - vertebral biopsies through echoendoscopic approach;
- further development of computerized tumor recognition programs and peripheral lung injury, by assisting with neural networks diagnosis and following up the patients with these types of disorders.

Until December 2019 it has been carried out an international grant program budgeted by the European Institute of Technology Health - Innostars (on the Horizon 2020 platform), where I am the responsible and the project manager from UMF "Iuliu Haţieganu", supporting the development of a medical software based on the analysis of transthoracic ultrasound images of peripheral bronchopulmonary masses for the purpose of positive and differential diagnosis. The scope is to determine the probability of malignancy, followed by the orientation of consecutive diagnostic procedures, but also monitoring the patients to reduce the use and exposure to ionizing radiation. This is an international priority, but also a future goal for me. Currently, we managed to establish a consortium with the LEITAT Institute of Barcelona and the University of Coimbra (Portugal), respectively the University Hospital of Coimbra, to prepare the implementation of an innovative project within the Horizon Europe program, based on the development of the prototype application with the creation of a usable version at the level of tertiary centers, for the monitoring of patients with bronchopulmonary tumors and other subpleural pulmonary disorders under various therapeutic modalities. In the letter of intent I also applied for the Start-up Amplifier option within the Innovation Projects - from Pillar III of the Horizon Europe / European Institute of Technology (EIT)

platform - Health. I have also applied to this session - October 2019 of the PN national competition with a new type of project PED (experimental demonstration project), as director, project oriented in the same research direction. All this research and applications are carried out in partnership with the Technical University of Cluj-Napoca. I submitted the documentation to OSIM for patenting the algorithm that I created for the transthoracic two-dimensional ultrasonographic diagnosis of peripheral lung tumors in 2018. I am involved, as a member of the research team, also in other projects submitted to national competitions.

I started a multidisciplinary collaboration with related specialties - internal medicine, cardiology, even with veterinary medicine, already publishing works and having in publication projects several articles (anomalies of the inferior vena cava system, isolated or combined with portal anomalies, cirrhotic cardiomyopathy, evaluation of complications of autoimmune type that appeared under immunotherapy in different types of malignancies - in collaboration with oncologists from several institutions). I formed a group of researchers (Dr. Georgiana Nagy, Dr. Vlad Ichim, Dr. Mihaela Mocan, Dr. Sonia Vlaicu) from the Medical Discipline I - Internal Medicine, Cardiology and Gastroenterology who are involved in the project initiated by me - application development for differential diagnosis and follow-up of patients with benign and malignant subpleural pulmonary disease, together with oncologists (Dr. Alina Florea). Other colleagues from the clinic add to this group (Dr. Roxana Chiorescu, Dr. Anca Fărcaş), but they also have their own fields of research in which I am involved.

My professional training included the understanding of a large number of applications of transcutaneous and transluminal digestive ultrasonography, accompanied by the acquisition of diagnostic and therapeutic endoscopic digestive techniques. Also, I learned and then developed multiple bioptic techniques of guided percutaneous ultrasonography as well as performing percutaneous ultraound guided drainages.

In perspective, I propose that the professional training include the following objectives:

- development of the personal experience in the use of contrast substances in ultrasonography, with its applications in gastroenterology as well as extradigestive (thoracic non-cardiac pathology);

- development of applications of endoscopic ultrasound fine needle aspirations in onco-diagnosis and other clinical indications (non-malignant conditions);

- further development and implementation in the hospital of echo-assisted interventional procedures and rendez-vous procedures with percutaneous echo-guided and transluminal endoscopic approach (transpapillary, etc.) combined under radiological guidance for biliary obstructions drainage and obstructions of the digestive tract;

- the practice and refinement of the preparation in digestive echoendoscopy, with all the applications that it allows, not only in digestive pathology;

- the training in interventional digestive endoscopy, including endoscopic retrograde cholangiopancreatography, activating as a major objective regarding the further development of the Gastroenterology Section and the Diagnostic and Therapeutic Digestive Endoscopy Laboratory of Cluj-Napoca County Emergency Clinical Hospital;

- attract several pharmaceutical companies and companies organizing clinical studies in order to carry out clinical studies within the SCJU Cluj, aiming to increase the prestige of the Hospital and of the group of the Gastroenterology Department, doubled by the funding of SCJU Cluj-Napoca.

The last section contains the bibliographic references mentioned in the chapters of the thesis, in the order of their appearance, in Vancouver style, followed by the annex which contains the abbreviations used.

I wish that by assimilating new knowledge and skills in accordance with the discoveries in the medical field, I will increase my performances in the fields of teaching, professional and research activity. I also intend to continue to contribute to the implementation of artificial intelligence in medicine, directly, by being among the first doctors in Romania to create diagnostic algorithms implemented in programming languages and then medical software.