GRIGORE T. POPA UNIVERSITY OF MEDICINE AND PHARMACY IASI

ADVANCES IN ENDOCRINE AND DIGESTIVE SURGERY

- HABILITATION THESIS -

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CONTENTS

ABBREVIATIONS

FNAC - fine needle aspiration cytology
MITS - Minimally invasive thyroid surgery
ANGPTL3 - proteins angiopoietin 3
ApoAV - apolipoprotein AV
trans-epidermal water loss – TEWL
parathyroid hormone – PTH
adenosine triphosphate – ATP
TNM - Tumor, Nodes, Metastases
parathyroid gland – PTG
World Health Organization – WHO
Thyroid Imaging Reporting and Data System – TIRADS
American Joint Committee on Cancer – AJCC
high density lipoproteins – HDL
low density proteins – LDL
chronic pancreatitis – CP
Resonant Recognition Model - RRM

REZUMAT

Cariera academică reunește sub egidea sa profesia de dascăl, cea de cercetător dar și pe cea medicală. Ea reprezintă vârful de lance în educație iar succesul său se bazează bazat pe perseverență și autodepășire, receptivitate și deschidere către idei și concepte noi. Flexibilitatea, dinamismul, spiritul și reflecția critică sunt de asemenea necesare. Impunerea și implementarea unor obiective și standarde profesionale în cariera academică este esențială și obligatorie în scopul asigurării creșterii continue a calității actului educațional și a rezultatelor științifice și chirurgicale.

La momentul actual cariera academică la nivel înalt inpune standarde pe măsură și subliniază conștientizarea necesității pregătirii continue, integrarea metodelor moderne în activitățile didactice și practica chirurgicală. Aceste criterii odată îndeplinite conduc către creșterea calității procesului educațional și a rezultatelor sale, la îmbunătățirea performanței științifice și la reușita în cariera chirurgicală.

Cariera unui profesor universitar are și trebuie să aibă un impact semnificativ asupra comunității academice. Aceasta trebuie să îmbine armonios o serie de aptitudini și calități, cum ar fi: cunoștințe științifice solide și permanent actualizate, disponibilitatea și plăcerea de a comunica și lucra în echipă, alături de dorința de a fi parte a unei echipe. La toate acestea se adaugă capacitatea de a crea și coordona structuri funcționale, bazată pe abilitatea de a identifica și motiva resursele umane prin propriul exemplu.

Teza de abilitare sintetizează întreaga mea activitate profesională, academică și științifică de după finalizarea cercetării doctorale. Ea este structurată conform criteriilor recomandate și aprobate de CNATDCU, în trei secțiuni majore.

În acest sens, lucrarea de față prezintă atât imaginea de ansamblu cât și cea detaliată a preocupărilor și obiectivelor principale din cariera mea academică de până în acest moment. Pe baza experienței personale în domeniile de interes voi detalia managementul proiectelor de cercetare pe care le am în desfășurare, alături de oportunitățile de studiu și de implementare pe care acestea le deschid.

Una dintre preocupările principale pe care o am încă de la începutul carierei mele academice este abordarea de noi domenii de cercetare cu implicație directă în practica chirurgicală și, în special spre beneficiul pacienților. Această preocupare se materializează acum într-o serie de proiecte de viitor pe care le descriu în secțiunea corespunzătoare a tezei.

În vederea obținerii atestatului de abilitare, manuscrisul de față rezumă activitatea mea de cercetare, didactică și medicală, efectuate din anul 1998 și până acum, an care corespunde finalizării și prezentării tezei mele de doctorat. Ea conține și descrieri detaliate ale proiectelor de cercetare viitoare pe care îmi doresc să le urmez în următorii ani.

Structura lucrării este împărțită în trei secțiuni principale: secțiunea I (SECTION I) care detaliază activitatea mea academică, chirurgicală și de cercetare, secțiunea a II-a (SECTION II) care așterne pe hârtie principalele rezultate ale activității mele de cercetare, materializate prin publicare de articole ISI cu factor de impact și secțiunea a III-a (SECTION III) care cuprinde referințele bibliografice din literatură.

Secțiunea I (SECTION I) prezintă rezultatele activității mele profesionale, științifice și academice în patru capitole și rezumă principalele contribuții personale din domeniul

chirurugiei endocrine și digestive, cele două mari domenii ale chirurgiei generale cărora le-am dedicat aproape întreaga mea carieră. Expunerea motivației personale în alegerea temelor de cercetare și drumul parcurs până șla implementarea acestora dezvăluie atât capacitatea de inițiere și dezvoltare a proiectelor de cercetare personală, cât și pe cea de a lucra în echipă. Scopul final al eforturilor și muncii desfășurate de mine și de echipele pe care le coordonez este beneficiul pacientului, în tot ceea ce înseamnă confort, reinserție socială, rezultate estetice deosebite postintervenționale și supraviețuire la distanță.

Aceste patru subcapitole sunt:

1. Privire de ansamblu asupra carierei și realizărilor profesionale
2. Activitatea academică
3. Activitățile științifice
4. Proiecte de cercetare

În primul subcapitol am expus aspectele cele mai semnificative și mai importante ale carierei mele de până acum și care aduc o plus valoare abilităților mele academice. Dorința de cercetare în sfera chirurgiei endocrine, digestive și a domeniilor conexe derivă din pasiunea pe care o am pentru această latură a medicinei și își găsește rădăcinile în întreaga mea carieră medicală.

Pe de altă parte, performanța atinsă în cariera chirurgicală se sprijină pe oportunitățile deschise în urma stagiilor de perfecționare medicală continuă pe care le-am urmat, în țară și în străinătate.

Cercetarea științifică pe care am avut-o până în prezent s-a materializat în publicații de cărți, articole și comunicări la congresele de profil. Toate acestea ascund în spatele lor o muncă asiduă de echipă și pasiunea pentru ceea ce facem. Diseminarea rezultatelor cercetării științice nu ar fi fost posibilă fără aportul formatorilor de școală medicală care mi-au coordonat cariera chirurugicală și academică și de la care am învățat această specialitate în domeniul chirurgiei generale.

Consider că nivelul academic pe care l-am atins asigură o vizibilitate internațională deosebită și, în mod direct, creșterea prestigiul Universității pe care o reprezint.

Tema aleasă pentru studiul doctoral și maniera și oportunitățile de continuitate a sa au deschis calea către cercetarea în sfera cancerelor colorectale și a pancreatitelor cronice. În cadrul studiului doctoral am deprins și mi-am perfectat abilitățile de cercetător atât de necesare carierei mele viitoare. M-am familiarizat cu tehnicile de diagnostic precoce, clinic și radiological al acestor patologii.

Cercetarea în această direcție s-a axat pe evidențierea mijloacelor moderne de diagnostic și stadializare precoce în cancerele colorectale și pancreatitele cronice. Elaborarea de modele de studiu ale etiopatogeniei și tipurilor evolutive ale acestor patologii, bazate pe animale de laborator sunt în actualitate și reprezintă unul dintre domeniile principale de interes din cariera mea.

Formulele matematice și fizice care caracterizează teoria haosului și proprietățile spectrale ale diverselor substanțe chimici și/sau structuri anatomice reliefează perspective noi în acest domeniu.

În partea a doua - SECTION II - am grupat realizările mele științifice și profesionale sub forma a două mari părți: *Abilități in chirurgia endocrina* și *Noi direcții în chirurgia tulburărilor digestive*.

Această abordare este motivată de către pasiunea pe care am avut-o dintotdeauna pentru chirurgia digestivă și, în special cea endocrină. Pentru a putea performa în orice domeniu este nevoie de a pune suflet în ceea ce faci și de a-ți actualiza în permanență cunoștințele în domeniu.

Aceste două ramuri ale chirurgiei generale au beneficiat, la rândul lor de aportul progreselor actuale din domeniile conexe: radiologie, tehnică de calcul, oncologie și bioinginerie.

Tendințele moderne centrate pe chirurgia miniminvazivă abdominală și a regiunilor anterolaterale ale gâtului presupune un antrenament adecvat pe aparatura necesară și o bogată experiență în domeniu. Rezultatele practicii curente chirurgicale se oglindesc în materialele publicate în reviste cotate ISI cu factor de impact.

În această secțiune a tezei am grupat sub forma coerentă a direcțiilor de studiu abordate cele mai semnificative articole publicate din cercetarea pe care am întreprins-o în chirurgia endocrină și digestivă.

Subliniez prezența în ambele părți ale acestei secțiuni a materialului care atestă interesul meu față de cercetarea metodelor noi de diagnostic precoce și stadializare ale acestor afecțiuni.

Sunt prezentate, de asemenea rezultatele cercetării personale în ceea ce privește rezultatele estetice ale chirurgiei regiunilor anterolaterale a gâtului și pe problematicile legate de particularitățile managementului pacienților din cele două categorii de boli.

Partea finală a ambelor subcapitole din această secțiune pune în pagină realizările personale în domeniile de nișă reprezentate de aplicabilitatea teoriilor și formulelor matematice și fizice cu aplicabilitate în domeniile mele de interes. Acest lucru se referă la aplicabilitatea teoriei entropiei fractale în diagnosticul și stabilirea prognosticului cancerelor tiroidiene și paratiroidiene. În ceea ce privește chirurgia digestivă, un interes particular îl am asupra metodelor de aplicare a analizei spectrale a markerilor neoangiogenezei tumorale în stadializarea cancerelor colorectale și a pancreatitelor cronice.

Capitol final al tezei - intitulat SECTION III - reprezintă suportul științific al activității mele de cercetare de până în prezent și baza viitoarelor mele planuri și proiecte de cercetare. Această secțiune cuprinde totalitatea referințelor bibliografice pe care mi-am clădit cunoștințele actuale în domeniile de interes și suportul actualizării permanente a acestora.

ABSTRACT

Academic career brings together the profession of teacher, researcher and medical practician. It is the top of the lance in educational system and its success is based on perseverance and self-indulgence, responsiveness and openness to new ideas and concepts. Flexibility, dynamism, spirit and critical reflection are also required. The assessment and implementation of professional goals and standards in academic careers is essential and compulsory in order to ensure the continuous increase in quality of the educational process and of the scientific and surgical results.

Nowdays, high-level academic careers meet standards and highlights awareness of the need for continued training, the integration of modern methods into teaching and surgical practice. Once these criteria are met, they lead to an increase of the educational process qualit and its outcomes, the improvement of scientific performance and the success in the surgical career.

The university professor career has and must have a significant impact on the academic community. It has to harmoniously combine a series of skills and qualities, such as: solid and constantly updated scientific acquaintance, availability and pleasure to communicate and teamwork, along with the desire to be part of a team. All this adds the ability to create and coordinate functional structures, based on the ability to identify and motivate human resources through their own standard.

The habilitation thesis summarizes my entire professional, academic and scientific activity after the completion of doctoral research. It is structured according to the criteria recommended and approved by CNATDCU, in three major sections.

In this respect, the present paper presents both the overall picture and the detailed overview of the main concerns and objectives of my academic career so far. Based on personal experience in areas of interest, I will detail the management of the research projects that I have in progress, along with the study and implementation opportunities that they open.

One of the main concerns I have since the beginning of my academic career is to address new areas of research with direct implications in surgical practice and, particularly, for the benefit of patients. This concern is now materialized in a series of future projects which are describe in the corresponding section of the thesis. It also contains detailed descriptions of the future research projects that I want to follow in the coming years.

In order to obtain the habititation certificate, this manuscript summarizes my research, didactic and medical work carried out since 1998, year which corresponds to the finalization and presentation of my PhD thesis.

The structure of the paper is divided into three main sections: SECTION I detailing my academic, surgical and research work, SECTION II, which maps on the main results of my research activity, materialized by publication of ISI rated articles with impact factor and SECTION III which contains the bibliographic references.

SECTION I presents the results of my professional, scientific and academic work in four chapters and summarizes the main personal contributions in the field of endocrine and digestive surgery. These are the two major areas of general surgery to which I have devoted almost my entire career.

Exposing personal motivation in choosing research topics and the way ahead and implementing them reveals both the capacity to initiate and develop personal research projects, as well as my teamworking abilities. The ultimate goal of the efforts and work carried out by me and the teams I co-ordinate is the patient's benefit in everything that means comfort, social reinsertion, distinguished postoperative aesthetic results and long tie survival.

On the other hand, the performance achieved in the surgical career is based on the opportunities opened by the continuous medical training courses that I have followed in the country and abroad.

The scientific research I have had so far has materialized in book publications, articles, and communications at congresses. All this hides behind the hard work teamwork and passion for what we do. The dissemination of the results of the scientific research would not have been possible without the help of the medical school trainers who coordinated my medical and academic career and from whom I learned this specialty in the field of general surgery.

I believe that the academic level I have achieved ensures a great international visibility and, directly, the prestige of the university I represent.

The theme chosen for the doctoral study and its manners and opportunities for continuity have opened the way to research in the field of colorectal cancers and chronic pancreatitis. In the doctoral study I learned and perfected my research skills so necessary for my future career. I have been familiar with the early, clinical and radiological diagnostic techniques of these pathologies.

My research in this direction focused on highlighting the modern means of diagnosis and early staging in colorectal cancers and chronic pancreatitis. The development of study models of the etiopathogenesis and evolutionary patterns of these pathologies based on laboratory animals are current and one of the main areas of interest in my career.

The mathematical and physical formulas that characterize the theory of chaos and the spectral properties of various chemical substances and/or anatomical structures reveal new perspectives in this field.

In the second part - SECTION II - I grouped my scientific and professional achievements in the form of two major parts: Prowess in Endocrine Surgery and New Directions in Digestive Disorder Surgery.

This approach is motivated by the passion we have always had for digestive surgery, and especially endocrine one. In order to be able to perform in any field, it is necessary to put some feeling into what you do and to constantly update your knowledge in the field.

These two branches of general surgery have also benefited from the current advances in related fields: radiology, computing, oncology and bioengineering.

Modern trends are centered on minimal invasive abdominal and neck's anterolateral areas surgery which require adequate training on the necessary equipment and a vast experience in the field. The results of current surgical practice are mirrored in materials published in ISI-rated journals with impact factor.

In this section of the thesis I grouped in the coherent form of the study directions the most significant articles published in the research we performed in endocrine and digestive surgery.

I emphasize the presence on both sides of this section of the material that proves my interest in researching new methods of early diagnosis and staging of these conditions.

The results of my personal research on the aesthetic results of neck's anterolateral regions surgery and on patient management specificities from the two main interest domains are also presented.

The final part of both chapters in this section puts into perspective my personal achievements in the niche areas represented by the applicability of mathematical and physical theories and formulas which fit my areas of interest. This refers to the applicability of fractal entropy theory in diagnosis and prognosis of thyroid and parathyroid cancer. Regarding digestive surgery, I have a particular interest in the methods of applying the spectral analysis of biomarkers fot tumour neoangiogenesis in the staging of colorectal cancers and chronic pancreatitis.

The final chapter of the thesis - entitled SECTION III - represents the scientific support of my research activity up to date and the basis for my future research plans and projects. This section contains all the bibliographic references that I have built up my current knowledge in the fields of interest and the support of their permanent updating.

SECTION I - PROFESSIONAL, SCIENTIFIC AND ACADEMIC ACHIEVEMENTS

1. CAREER OVERVIEW AND PROFESSIONAL ACHIEVEMENTS

The development of my career is based on both a professional and an academic part. These sides are the cumulative and qualitative result of personal experiences of life. Efforts to achieve a high level of performance and academic recognition are successfully equalized by results in surgical practice.

From a surgical experience of more than 34 years, 26 have been complementary to my academic career. Thus, the results of academic career integrate into the complexity of the requirements and exacting standards of the medical and of the research activity. Throughout this period, I have gained experience in managing student series, working with residents doctors, and also with regard to my main goal - digestive and endocrine surgery.

The research perspective of this surgical subfield has stimulated me throughout my university career and has focused on medical and surgical activity in order to ensure a higher quality of interventional procedure. This theme has a major social and economic impact. The research directions we have carried out so far address mostly to the decrease of the operative time, the incidence of immediate and remote post-interventional complications and the obtaining of an aesthetic result as good as possible.

In this regard, I have performed more than 20000 surgery procedures, as an operator or team member and over 9000 interventions in the endocrine field. I did the first peritoneovenous shunt (also called LeVeen Shunt) and the first thoracoscopic sympathectomy in Romania. The experience gained in endocrine surgery has led me to be the promoter of total thyroidectomy in the polynodular goiters. I have also initiated several surgical techniques at the Clinic in which I practice: the first laparoscopic suture of a perforated ulcer, the first laparoscopic splenectomy, the first laparoscopic suprarenalectomy, the first thoracoscopic timectomy and the first thoracoscopic sympathectomy.

As a founding member and president of the Romanian Society of Endocrine Surgery, I was nominated as a national delegate of ESES (European Society of Endocrine Surgery).

The main future goals of my professional career are to continue the research in directions mentioned above; in the short and medium term it is a priority to establish new research opportunities and topics such as minimally invasive neck surgery and surgical treatment of late complications in acute and chronic pancreatitis.

At the same time, the significant efforts made by me and the medical team I coordinate also focus on the complex study of endocrine tumour pathology through modern early diagnosis techniques. We anticipate that the results of this study will materialize through reference publications and would be an extremely valuable tool in assessing the socio-economic, demographic impact and in developing a management protocol that is so necessary for these patients.

In parallel and in close connection with thyroid surgery, I have developed experience in the parathyroid gland surgery.

I intend that all these efforts to have the expected impact and be able to attract as many colleagues as possible, in order to coagulate several elite, multidisciplinary medical centers that should be also medical centers for training in the same directions, both in the medical act as well as the research. Without such collaborations and without the human resource, our research in the mentioned areas would not be possible.

The assiduous work and the passion for it represent the foundation of my academic career, along with awareness of the research importance and the opportunities offered by training sessions in the country and abroad. This step towards exchanging experience and research with international prestigious centers of excellence is of paramount importance to inform us about current trends and latest developments.

I consider it a great opportunity to link the three major aspects of my career - didactic, surgical and research - around the main theme of concern - endocrine surgery - which brings together all the others .

2. ACADEMIC ACTIVITY

I begun my university career in 1993 as an assistant professor, position gained through contest in the Department of Surgery at the Faculty of Medicine of the "Grigore T. Popa" University of Medicine and Pharmacy (UMF) in Iasi. Since 2003 I have been associate professor in the same department. In recent years I also coordinate the Ist Department of Surgery, as a director at UMF Iasi.

The activity as Head of 4th Surgical Unit of the "Sf. Spiridon" Emergency Hospital Iasi represent a significant part of my activity so far.

The medical practice for more than 34 years, together with an academic experience of more than 26 years, gave me the skills necessary in the activity of guiding the future physicians, as well as the scientific research. I had the opportunity to form myself from an academic point of view and, implicitly professionally in national and international recognized centers under the coordination of elite personalities in the surgery.

To all these must be added participation in postgraduate training in the subfields of interest materialized by obtaining professional attestations that allow me to practice the maneuvers and techniques necessary in my practical and current research:

- Course of peripheral vascular surgery - H. Van Gesten, mai 1992 Belgium;
- 2nd advanced postgraduate course of gastroenterology and digestive surgery - March 1993 Holand;
- ATLS (advanced trauma life support) course - Peter Driscoll (Manchester) – april 1995 Brasov;
- Laparoscopic surgery course - prof. Bancewicz (Manchester) - mai 1995 Iaşi;
- AFSA (equivalence of competence) in cardiothoracic and endocrinological surgery - nov.1995 - nov.1996 Claude Bernard University, Lyon, France;

- 15th International Course on Gastrointestinal Surgery - Feb.1998 Davos Switzerland;
- November 1995 - October 1996 two training sessions in cardiothoracic and endocrinological surgery in Lyon, France, where I assisted and operated about 300 cardiovascular patients, including heart, pulmonary, thoracic and thyroid transplantation;curs de management Eurocor 2011 - 2012;
- Practical course of thyroid and parathyroid surgery - November 2012 Harvard Medical School, Boston;
- Actualities in health management - 2015 UMF "Gr.T.Popa" Iasi;
- Minimally invasive endocrine surgery course - 2016 IRCAD / University of Strasbourg, France.

The impact on the current medical practice of these professional competencies was also reflected in my scientific research, where it has been materialized by publishing ISI quoted articles with an impact factor.

In the same main direction, I also focused the didactic activity, supported by the personal medical results, and I consider the role and the responsibility that we have as medical school creators as fundamental. I consider that we must fight to stimulate, encourage and train future doctors in exploring these themes.

My academic activity has materialized over these years on appreciation of the importance of the role of the teacher as a factor of change that promotes understanding and tolerance. That is why the teachers responsibility is enormous, because they are among those who participate in the formation of the characters of the new generation and should be models for the students.

Under the current conditions in which the contemporary world is evolving at such an alert rhythm, there is a clear need for updating and continually improving the level of knowledge and teaching techniques that we use. However, knowledge-based society presupposes to generate informations, especially through scientific research, their transmission through education and training, their dissemination using means of information and communication technology, the valorisation of knowledge through technological innovation.

Also, the patterns identified as a result of analyzed needs and student opinion tests have shown the need to orientate university activities especially on the student by using active-participatory strategies, the application of academic group management and the diversification of assessment techniques with orientation on student's performance and skills. This approach involves a well-established route, characterized by defining objectives of didactic activity and finding ways to achieve them through various activities, which in short means student centered education.

These things have made me pursue along time the consolidation of the education process and continuous qualitative improvement in accordance with the requirements of the national education system as well as the international requirements.

3. SCIENTIFIC ACTIVITIES

Through my research work in my career, I have pursued the continuation and finalization of research projects and involvement in new ones.

A very important aspect is to develop the research results by publishing studies and articles. In achieving this goal it is necessary to develop research through interdisciplinary initiatives and expand collaboration to develop research projects.

I have always considered it essential, the attraction of an increasing number of students and master students in scientific research. In this respect, I launched the Master Study on the "Surgery in Thyroid Pathology", which I coordinate.

The ultimate goal of the whole research activity is to increase visibility at national and international level.

Starting from the premise that academic cooperation is an essential part of the research strategy, the development and diversification of collaborations with teaching staff / researchers from other university centers in the country and abroad have been and are a constant concern for me.

The constant involvement in research and didactic work through scientific projects, guiding students and resident doctors, is a long-term guarantee of academic and surgical skills and professionalism.

The fact that I coordinated several medical teams during my years of experience in surgery and collaboration with other reference centers in the country and abroad has made my training as a researcher possible and have provided me with extensive experience in the field.

The novelty of my research activity is given by its direct and implicit clinical applicability and the adaptability that I and my team have shown in addressing new techniques and surgical principles. We have succeeded in the orientation and restructuring of each study that we conducted according to feedback received in real-time from the subjects, information that we have interpreted and analyzed.

Careful monitoring of patients, both in hospital and remotely, has made it possible to obtain a valuable database with a strong research potential in future studies. Personally, I consider it a necessity and a plus of mandatory and inherent value of my research activity to win and implement, national and international research projects.

4. RESEARCH PROJECTS

Until now, we have performed retrospective and prospective clinical studies on groups of statistically significant patients in endocrine and digestive surgery.

The results of these studies were disseminated by publishing articles in ISI quoted journals with impact factor and communications at congresses and conferences.

The private grant award project attributed by the competition entitled "REGEN-SIL Performance in the Prevention of Scars after Incisions in the Anterolateral Cervical Region"

aimed at achieving the postoperative cosmetic desideratum in the anterolateral neck surgery. The main beneficiaries of my research activity and of my projects are and must be patients.

Considering my personal, surgical and scientific experience, I intend to address the related research areas to my previous work. Thus, I consider it a great opportunity to study the modern management and control techniques of the endocrine oncology patient at a distance from the surgical moment. In this direction I will study the fractal analyses and spectroscopy and the real possibilities offered by them in monitoring the effectiveness of oncology treatment.

As I have already mentioned, I orientated all my work and efforts in the field of digestive and, especially, endocrine surgery. Within these domains we have conducted cohorts and multicentre studies on large groups of patients. Thus, I divided my work into two main areas: first of all, the field of endocrine surgery, focused on thyroid and parathyroid surgery and the second one, the field of digestive surgery, which focuses on the prophylaxis and treatment of pancreatitis and colorectal cancers.

The goal to deepen research into minimally invasive thyroid surgery will be put into practice by applying for Grant research projects on this topic. I intend to get funding in this direction through national and international projects.

Obtaining these results means the recognision of my experience and the team I coordinate in this area. The anticipated impact of implementing new research directions on academic career and personal international visibility is extremely important. It offers the opportunity to obtain the funding for these objectives and the dissemination of the obtained results.

As all of us know, endocrine surgery is continously evolving, with new technologies and approaches appearing on a regular basis. Meanwhile, just a few of them become part of our standard surgical guideline and many others do not last for long. Each of the new contributions are highly optimistic at their begining, but time and further studies end up determining the exact role they play on endocrine surgery, lowering the initial promising prospects.

Based on professional experience in this field, we have chosen two perspective topics: the use of indocyanine green (ICG), owing to its new role helping us to evaluate intraoperatively parathyroid function and maybe allowing us to take “ad hoc” decisions; the hemithyroidectomy through an axillary laparoscopic approach.

We will regard to research these future project by exploring and experiencing theirs indications, advantages and disadvantages using patient screening and professional training.

In the same order we shall drawn on guests of the highest caliber, with longstanding experience on endocrine surgery, whom all master the topics to be discussed and performed together.

In the recent years, the protocols for the management of thyroid nodules and thyroid cancer have changed with new perspectives for the future. With the implementation of a consensus and a guideline for the management of thyroid nodules and thyroid cancer consideration of a more conservative approach for most patients with thyroid nodules have been taken into account. These refer to the cytologically indeterminate on fine-needle aspiration biopsy and benign according to gene-expression classifier results.

In the immediate future we also consider to proceed exploring the assumptions came from the outcomes of cutting-edge studies that propose the use of recombinant human TSH and low 131 I dose, 30 mCi (1.1 GBq) for post-operative ablation. This coluld be sufficient for the management of low-risk thyroid cancer.

Coding the signalling cascade proteins that are mutated or aberrantly expressed in thyroid cancer is another perspective of our activity which will allow to investigate tumour biology. This technique would allow us to select different drugs according to several potential targets for therapy have been defined in Differentiated thyroid carcinoma, medullary thyroid cancer and even in anaplastic Thyroid Carcinoma, and these drugs represent new therapies for advanced thyroid carcinoma.

In less than a decade and despite numerous setbacks, Robotic Thyroid Surgery became the most desired immediate perspective and most of the countries. Initially encountered issues are mostly related to costs, the body size and cultural perceptions.

Advantages over the transaxillary approach include the reduced flap area and the obviation of the risk of brachial plexus injury. Even though it is considered a "more natural" approach, the retroauricular robotic thyroidectomy is leveled 3 at present with a small number of studies to date and an associated limited uptake of the technique. The latest development in the field relates to transoral robotic thyroidectomy.

Larger, comparative studies are needed to establish its role in modern thyroid surgery and bringing a surgical robot at our disposal is one of our main focuses and challenges. Robotic thyroidectomy is a complex and technically demanding operation that requires intensive training and proctorship for its safe implementation combined with careful patient selection. At this time long-term outcomes are already starting to emerge in the literature and predict a promising future for robotic thyroidectomy.

The immediate estimated impact of future research is primarily a human one to reduce the mortality and rate of postinterventional complications due to endocrine cancers.

At the same time, the future studies results are directly applicable to my academic career in order to stimulate medical students which intend to follow a career in endocrine surgery.

In order to achieve the expected results it is necessary to follow the subjects from the study groups for a period of at least 5 years and to adjust their management protocol.

Continuing research in the field of endocrine surgery is required to be done through a similar approach to the initial one, by studying a large group of patients and by initiating multicentre international studies.

SECTION II – SCIENTIFIC AND PROFESSIONAL ACHIEVEMENTS

1. ADVANCES IN ENDOCRINE SURGERY

1.1. STATE OF THE ART

Endocrine surgery is a specialty that includes surgical procedures for thyroid gland, parathyroid glands, adrenal glands, endocrine pancreas and some neuroendocrine glands. It is an integrated field in general surgery.

The concept of endocrine surgery was introduced relatively recently, at the beginning of the 20th century, being marked by the physiological theories of the Russian scientist Ivan Pavlov (Horsley, 2019). He argued that the nervous system primarily controls all the corporal activities and that there are few endocrine glands without duct (Welbourn, 1990).

William Bayliss and Ernest Starling made a simple discovery in 1902, that gave rise to the science of endocrinology, demonstrating that intestinal acid stimulated pancreatic juice secretion when all connections from both organs to the nervous system were separated. They sustained that a "chemical" substance, rather than a "nervous" substance, is responsible for pancreatic secretion and named it secretin. The discovery of secretin made Starling propose the term hormone derived from a Greek word that means "excite" - substances that mediate circulatory messages (Bayliss and Starling 1902). Langerhans previously assigned an endocrine function to the pancreas islets and thus it was born the endocrinological science (Langerhans, 1869; Unger et al., 1963).

The development of endocrine surgery as a distinct branch of medical science has been made rapidly and many researchers have won Nobel Prize for Medicine. Thus, surgeon Theodor Kocher won the Nobel Prize for his observations on physiology, pathology and thyroid gland surgery. He was also the first to notice that total thyroidectomy is associated with mixedem, and this can be prevented by subtotal thyroidectomy (Norton, 2008). He operated 10 000 patients for thyroid disorders, a target which I am very close to reach (9500 thyroidectomies).

Kendall, a Mayo Clinic chemist, has been able to isolate thyroxin from the thyroid gland, then Banting and Best have extracted insulin from the pancreatic islets (Norton, 2008).

For a long time, the understanding of the integration and interaction of the various endocrine glands was unclear. Walter Cannon was the one who noticed that emotional stimuli caused the secretion of the adrenal medulla, which he described it as part of both endocrine and nervous system. Loewi showed that the neurotransmitter secreting cells were present in the hypothalamus, with neurohormonal control on the pituitary gland and that their secretions were controlled by the hypothalamus (Norton, 2008).

Important neurohormonal systems such as Kulchitsky cells of Masson have been identified as involving neurons, enzymes, peptides and amines. It have been shown to have important features, including amine manipulation and peptide production. He invented the

APUD notion, i.e. the absorption of the amine precursor and the decarboxylation (Pearse and Churchill, 1953).

Berson and Yalow have developed a simple quantification of minimal amounts of circulating hormones through the progress of radioimmunological tests - RIA, which has allowed accurate diagnosis of endocrine disorders (Berson and Yalow, 1960).

Modern endocrine surgery has been developed with the primary goal of curative treatment of endocrine tumours and other diseases that cause excessive glandular hormone secretion.

At the same time, the development of hormone substitution therapy has an important role in the treatment of endocrine disorders associated with low levels of hormones.

Endocrine surgery is a subfield area of general surgery in which I have focused on the cervical segment. Surgery of thyroid and parathyroid glands is, in turn, a segment in full ascension and a subject of great interest in scientific research. It also has an important social impact.

Current research directions in this field seek to find methods of minimally invasive surgical approach to anatomical structures in the anterolateral neck region. These surgical techniques should have lower surgical complications and better oncological, functional and aesthetic results.

Thyroid gland surgery is the largest part of endocrine surgical procedures worldwide and is my main area of interest. It concerns both malignant and benign pathology with surgical indication.

Thyroid surgery has an illustrious past, probably starting with Albucasis, which made the removal of a major goiter in 952 AD.

At one point in history, thyroid surgery was considered a frightening and blurred procedure. Surgeons like Theodor Billroth and his student Theodor Kocher ventured into this surgical field and mastered it, popularizing it and destroying all fears about a dreadful result. Classical thyroidectomy, in its various forms, has developed since then, and now attempts are made to perform the surgical procedure in a minimally invasive manner (Sarkar, 2016).

The occurrence of this subfield took place in the United Kingdom, where Dick Welbourne and John Lynn developed it as a proper specialty separated by general surgery, at the Royal Postgraduate Medical School. Surgery procedures involved total or partial removal of the thyroid gland (total thyroidectomy, lobectomy or hemithyroidectomy). Incomplete resections (subtotal or almost total thyroidectomy) are also practiced but they are not agreed by most surgeons (Jeffrey et al., 2011).

Around 2700 BC, the Chinese used burned sponge and seaweed to treat goiters. Pliny the Elder noted epidemic outbreaks in the Alps and also mentioned the use of burned algae in their treatment. They were supposed to have learned this treatment measure from the Chinese. The term goiter comes from neck swelling (goitre) as "galaganda". The oldest anatomic image of the thyroid gland was made by Leonardo da Vinci in 1511 during the anatomic studies in Florence (O'Malley, 1925). It assumed that the purpose of the gland was to fill the space caused by a muscle deficit, thus making the trachea position far from the stern (O'Malley, 1925).

Exophthalmia has been described for the first time by Caleb Hiltier Parry of Bath in 1768, in his writing "Expansion of the thyroid gland in connection with heart enlargement or

palpitation". This subject was then further examined by Robert James Graves and Carl Adolf von Basedow, who published their observations independently in 1835 and 1840 respectively (Parry, 1825).

Their publications focused on the association of goiters with exophthalmia, palpitations, irritability, weight loss, wild hunger, hyperactivity, heat and sweat (Graves, 1838; von Basedow, 1840).

In the seventh century, a classical Byzantine doctor, Paul de Aegina, described the stroma and the functioning of the thyroid gland (Haeger, 1988).

The earliest reference of a successful attempt to surgically treat goiters belongs to physician Ali Ibn Abbas (Albucasis), around AD 952. He used opium for anesthesia and simple ligatures (Amr, Tbakhi, 2007).

In 1170, at the Salerno school, surgeon Roger Frugardii performed a thyroidectomy using filaments, hot iron, ligaments and caustic powders. He wrote the book entitled "Practica chirurgiae", which became a principle of surgery in the thirteenth and fourteenth centuries (Corner, 1931).

When the church began to control the Legislation of Universities, progress began to decline, discouraging medical activity, especially surgery. Libraries have avoided books on surgical works, and faculties have stopped training surgeons under the motto "Ecclesia abhorret e sanguine" meaning "the church takes care of the blood" (Brzeziński, 2004).

In the late Middle Ages, surgery was redeemed with the efforts of Guy de Chauliac and others like Henry de Mondeville or Guido and Bonetus Lanfranchi. They have used the teachings of Albucasis and Roger Frugardi.

During the Renaissance, a great surgeon Ambrois Parre contributed substantially to the progress in thyroid surgery. In 1791, Pierre Joseph Desault performed the first partial thyroidectomy, followed closely by surgeons from Dupuytren's school.

The diagnosis has become more accurate with advances in modern radiology, such as ultrasound scanning and computerized tomography, along with the introduction of fine needle aspiration cytology (FNAC) in 1952, as described by Soderstorm (Mathur, 2010).

Along with advances in other disciplines of medical science such as anesthesia, physiology and radiology, surgical treatment of thyroid disease has improved significantly. The parathyroid glands transplantation, that were accidentally removed during thyroid surgery, has also given new perspectives in total thyroidectomy procedures.

In addition to making the surgery safe and effective, the current direction of thyroid gland surgery focuses in particular on achieving the best cosmetic techniques and overcoming other shortcomings.

Minimally invasive thyroid surgery (MITS) is a recent study direction. This type of surgery is well accepted in other surgical specialties, but in head and neck surgery, it was introduced quite slow (Mouret and How, 1996).

These procedures can be categorized as pure endoscopic techniques, assisted video open minimally invasive surgery and also robotic surgery, not yet accepted by the FDA.

Endoscopic technology also differs in terms of different pathways used for thyroid approach and also depending on whether or not carbon dioxide is used. The access ways are the lateral side of the neck, axilla, anterior thorax (Ikeda, 2000, 2004; Inabnet and Gagner 2001; Takami, 2002; Terris, 2005).

Miccoli and his team have found that MITS is as effective as conventional surgery, with a 2-3cm postoperative scar, in carefully selected cases of papillary thyroid carcinoma and in most benign cases with a volume under 30ml. There is no significant difference between the two groups in terms of iodine uptake or circulating thyroglobulin concentrations (Miccoli, 2002; Wirth et al., 2011).

Thyroid surgery is closely related to that of parathyroid glands and vice versa. Both types of endocrine surgery are the main focus of my professional work.

Although in this thesis we focused on reimplantation of parathyroids removed accidentally during a thyroididectomy or primary hyperparathyroidism surgery, my current concerns aim at obtaining the minimal functional, oncological and aesthetic necessary resection, as well as preserving the phosphoalkalic balance.

Thyroid hormones influence major metabolic functions, mainly by increasing basal energy gain. They act on the metabolism of proteins, carbohydrates and lipids.

Thyroid hormones influence the synthesis, mobilization and degradation of lipids, although degradation is influenced more than synthesis. The main and most known effects on lipid metabolism include the increased use of lipid substrates, increased synthesis and mobilization of stored triglycerides in adipose tissue, increased unsaturated fatty acid concentration, and increased lipoprotein lipase activity.

Thus, severe hypothyroidism is commonly associated with increased serum cholesterol and iatrogenic lipoprotein levels. Even in the case of subclinic hypothyroidism, which is characterized by increased serum TSH levels with normal serum thyroid hormone levels, there is a slight hyperlipidemia that increases the risk of atheromatosis (Pucci, 2000).

Thyroid hormone action on triglyceride metabolism includes both de novo lipogenesis by transcription of several key lipogenic genes as well as increased hydrolysis. Lipid hydrolysis is regulated by LPL and HL activity, the enzyme that converts intermediate density lipoprotein (IDL) molecules into LDL. Regarding LPL, it has been reported that T3 can stimulate its activity both by high regulation of apolipoprotein AV (ApoAV) and by lowering the level of proteins angiopoietin 3 (ANGPTL3) inhibitory (Sinha, 2018; Kuusi, 1988; Valdemarsson, 1987; Tan, 1998; Prieur, 2005; Fugier, 200).

Thus, an explanation for the increase in plasma TG levels in hypothyroidism is the decrease in the clearance of TG-rich lipoproteins by low enzyme activity. In this context, a decrease in HL activity in SCH was reported in association with the degradation of the chemical composition of isolated LDL particles due to TG enrichment in middle-aged women with SCH. HL activity was subsequently found to be inferior in the presence of VLDL / IDL residues, which are identified by an electrophoretic qualitative method in patients plasma (Brenta, 2007; Duntas, 2018).

These serum variations of two molecules that enter in the cholesterol structure represent an example of a non-differentiated model and, theoretically can be evaluated by applying fractal entropy calculation formulas. This is achievable by radiological labeling of these molecules and interpretation of fIRM results.

The incidence of postsurgical hypoparathyroidism was effectively reduced by applying a technique to protect blood flow to the upper parathyroid glands during thyroid cancer surgery (Kong et al., 2019; Cetin et al., 2019).

The medical history of parathyroid gland research is fascinating and full of famous medical names. This discovery was followed by laborious research parathyroid anatomy, embryology and pathology, and in the physiology of calcium metabolism. All this led to the production of hormonal substitutes drugs and, finally, to the improvement of surgical techniques.

In 1850, Sir Richard Owen was to identify these glands for the first time, but their current name was first used - "glandulae parathyroideae" - in 1880 (Sandström, 1880; Wolfer, 1882).

The parathyroid hormone physiology and calcium and phosphocalcic metabolism has raised the interest of mentors in thyroid surgery for many decades. This is still happening today (Giddings et al., 2009).

Initially, the patients were treated as medical curiosities and documented as patients without a possible medical treatment or having unexplained surgical complications after thyroidectomy. Halsted observed "the disastrous results of loss of the glands" and the resulting tetania, as did Billroth. They were among the founders of modern endocrine surgery (Organ, 2000).

The purpose of my research in this field, conducted by myself and the team I co-ordinate, is to present the results of technical and clinical studies related to thyroid and parathyroid gland surgery. In these studies we approached issues related to diagnosis, treatment options as well as the ethical and social problems of benign and malignant thyroid and parathyroid pathologies.

We correlated this results with the latest knowledge of thyroid hormones and thyroid diseases and any other related areas, thus including a wide range of thyroid topics, such as diagnostic methods, pharmacology, invasive treatments, physiological mechanisms and thyroid hormone regulation, immunological aspects, genetics, new trends in disease management, thyroid disease and complications.

The implications of our studies are mainly prospective because they open the way to future research in this field.

"*The history of medicine is, in fact, the history of humanity itself, with its ups and downs, with its courage, aspirations for truth and purpose, its pathetic failures. The subject can be treated differently as a mystery, a series of books, a succession of characters or Theories, an Expansion of Humanity*" Edward Delos Churchill.

This research direction has been materialized by publishing the following articles:

1. **Grigorovici A,** Bacaita ES, Păun VP, Grecea C, Butuc I, Agop M, Popa O. Pairs generating as a consequence of the fractal entropy: theory and applications. *Entropy* 2017; 19(3), 128, DOI: 10.3390/e19030128.
2. **Grigorovici A**, Costache M, Velicescu C, Savin G, Ciobanu D, Preda C. Radical neck dissection in advanced thyroid cancer. *CHIRURGIA* 2010; 105(5):669-672.
3. **Grigorovici A,** Varcus F, Mogoș S, Călin A, Hînganu D, Hînganu MV, Preda C. Hypocalcemia after thyroidectomy for advanced local malignancies. *Rev Chim Bucharest* 2019; 70(3):1053-1057.
4. Andronic D, Velicescu C, Bulimar V, Hînganu D, Călin A, Hînganu MV, **Grigorovici A**. Assessment of phospho-calcic metabolism in parathyroid tumors. *Rev Chim Bucharest* 2019; 70(2):705-707.
5. **Grigorovici A,** Cherciu MS, Popescu CM, Apostol DGC, Preda C, Calin A, Aelenei P. Efficacy and safety of regen-sil in post-operative scars management. *FARMACIA* 2017; 65(1):29-39.
6. Varcus F, Ciobanu GD, **Grigorovici A**, Hînganu MV, Hînganu D, Leuștean L. Biochemical markers in nodular goiter in children. Indications, methods and outcome of the surgical treatment. *Rev Chim Bucharest* 2019; 70(3):996-999.

1.2. PERSONAL EXPERIENCE IN NECK RADICAL DISSECTION APPLIED FOR ADVANCED THYROID NEOPLASIA.

1.2.1. Introduction

Thyroid cancer is a rare malignant tumour, but is the most common cancer of the endocrine system. It affects women more on a age of 25-65 years (Bailey, 2001). The most common type of thyroid cancer is represented by papillary thyroid carcinoma, approximately 85% of all thyroid cancer (Pearce et al., 2004). Most of the papillary thyroid cancer shows good prognosis but some of them has aggressive behavior such as local invasion, lymph nodes extension or distant metastasis (Gulben et al., 2008). There are various factors which have been known to be associated with prognosis of thyroid cancer: age, gender, tumour size, extrathyroid extension and distant metastasis (Passler et al., 2004; Joo et al., 2015).

The most effective treatment for thyroid cancer is surgery which involves various techniques.

Radical neck dissection has an important role in the surgical management of cervical carcinoma. It is used especially to control cervical lymph node metastasis (Razack et al., 1981; Razack et al., 1979).

Nodal metastasis occurs in more than 70% of patients with medullary thyroid carcinoma (MTC) with a palpable primary tumour; total thyroidectomy and bilateral neck dissection is recommended as minimal surgery (Ahn and Chung, 2019).

The concept of ”lymph node removal” in thyroid cancer was introduced for the first time by Kocher in 1880. Classically, the technique of radical neck dissection was described later (1906) by George Crile and consisted of removal of lymph nodes from levels I to V and resection of the spinal accessory nerve, the sternocleidomastoid muscle, and the internal jugular vein (Crile, 1906).

The 1960s and 1970s were marked by a significant change in the treatment of malignant cervical disorders. This can be exemplified by conservative surgery (with tissue preservation and implicit function) that developed new surgical techniques. In 1953, Pietrantoni, a sustainer of elective bilateral dissection of the neck, nevertheless recommended the maintenance of accessory spinal nerves and at least an internal jugular vein (Muller et al., 2002; Edis, 1977).

An Argentinean surgeon introduced the concept of modified neck dissection. It involved the removal of nodes, but with preservation of one or more of the following structures: the internal jugular vein, the accessory nerve and/or the sternocleidomastoid muscle (Ferlito et al., 2004). Later it was described the functional neck dissection. This tehnique involved a modified neck dissection with preservation of the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein. Functional neck dissection have less morbidity than radical neck dissection, but the same oncological outcome (Bocca, 1975; Welch and McHenry, 2013).

After this surgical procedure, a multitude of modified techniques, as specific as possible for the incipient stages of cancer, have developed. In 1989 Medina suggests that lymphadenectomies can be comprehensive, selective or extensive. In 1991, Robbins used the term "selective" to distinguish patients to which it was preserved at least one nodal group. There are still debates over terminology and techniques.

Tisell et al. described microsurgical lymph node dissection in 1986 (Tissel et al., 1986). However, this procedure was quite labor-intensive at that period and took more than 5hours at that time. Furthermore, otherstudies reported that even with extensive neck dissection, a biological cure is rarely achieved in patients who have more than 10 positive nodes or more than 3 compartments involved (Machens et al., 2000; Weber et al., 2001; Ahn and Chung, 2019).

Nowadays, the management of clinically positive lymph nodes in thyroid cancer involves the modern modified radical or functional neck dissection, which means removal of lymph nodes from levels II toVI. Level I lymph nodes are not routinely removed because they are rarely involved in thyroid cancer (Welch and McHenry, 2013).

Papillary thyroid carcinoma, Hurthle cell, and medullary thyroid carcinoma usually metastasize to cervical lymph nodes. Studies reported that almost 35% of patients with papillary thyroid carcinoma and 75% of patients with medullary thyroid carcinoma will present clinically evident cervical lymph nodes metastases (Schlumberger, 1998; Kloos et al., 2009). Patients with thyroid cancer and macroscopic lymph node metastases will undergo surgery. It will be performed a lateral compartment neck dissection (Welch and McHenry, 2013).

Studies registered an increased mortality rate in patients over 55 years of age, with differentiated thyroid cancer and regional lymph node metastases (Lundgren et al., 2006; Welch and McHenry, 2013).

There have been a lot of debates over the influence of prophylactic or therapeutic cervical lymphadenectomy on prognosis, such as recurrence or survival rate for the thyroid cancer patients with or without limph nodes metastasis (Attie, 1988; DeGroot et al., 1990; Joo et al., 2015). Many studies reported higher frequency of recurrence in patients found to have limphatic nodes metastasis at the time of initial surgery with no significant change in overall survival, while some report decreased disease free survival (Attie, 1988; DeGroot et al., 1990; Joo et al., 2015). While lymph node metastasis may not influence overall survival, it presents a significant risk of regional recurrence which diminishes quality of life during periods of recovery after initial treatment (Joo et al., 2015).

In the absence of alternative effective treatments, surgery combined with postoperative radioiodine treatment continues to be the first choice for thyroid cancer patients with bilateral neck metastasis. Researchers believe that a more complete resection results in greater success (Guo et al., 2018).

Total thyroidectomy with or without limited lymph node dissection is an ideal solution in thyroid cancer with long-term average results. In this study we want to highlight the better prognosis of patients with advanced thyroid cancer that underwent tihyroidectomy associated with radical or radically modified neck dissection.

Our aim is to assess the most important medium and long term advantages and disadvantages of the technique of radical neck dissection in cases of interventions for thyroidectomy within limits of oncological security.

1.2.2. Materials and methods

1.2.2.1. Study group

We retrospectively reviewed the medical records of patients admitted to the III-rd Surgical Unit of ”St. Spiridon” Emergency Hospital Iași, between January 2000 to September 2009. The patients presented for the treatment of malignant thyroid disorders. The evaluation of the results was done with data from the subsequent surgical follow-up. All patients were investigated and diagnosed during prior admissions at the Endocrinology Clinic or the Otorhinolaryngology Clinic.

The study group comprised 140 women and 49 males (W: M ratio = 2.85). Distribution by age group reveals a maximum incidence of thyroid cancer in the sixth decade of life, with an average of 51.48 years (extreme 19-81 years) (**Figure 1**). We used the staging of TNM set by AJCC (Bychkov, 2019). (**Table 1,2**) Anaplastic carcinomas are considered at stage T4. Regional lymph nodes are those in the median and lateral cervical compartment and superior mediastinum (**Table 1, 2**).

1.2.2.2. Methods of treatment

In the Third Surgical Unit were performed during this period 189 interventions for malignant thyroid disorders, of which 59 total thyroidectomy with radical/radically modified neck dissection and 34 with selective dissection in central or lateral neck compartment. The

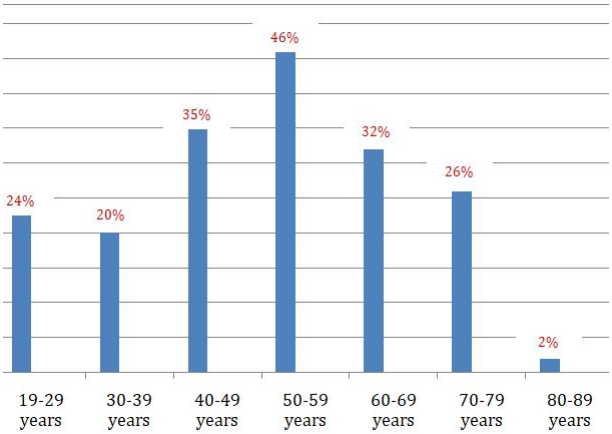


Figure 1. Distribution by age groups of patients with thyroid neoplasm

surgical technique consisted of total thyroidectomy accompanied by radical neck dissection, which included the lymph nodes removal of the lateral or median neck compartment, the resection of sternocleidomastoid muscle, subhioid muscles, recurrent nerve when it was embedded in the tumour, resection of the clavicle (for approaching the upper mediastinum) and the internal jugular vein, possibly carotid adventitious, using 48-hour thyroid aspiration drainage. In the absence of complications the patients left the hospital on the third postoperative day. All patients received thyroid stimulating hormone suppressive hormonal therapy and radioactive iodine therapy after surgery.

1.2.2.3. Follow up

Long-term follow up was done at 6, 12, and 24 months in Third Surgical Unit and Endocrinologic Unit, where hormone replacement therapy and radioiodine therapy (selected cases) were initiated. If routine tests indicated recurrence, enhanced CT was performed to confirm if additional surgery was needed.

1.2.3. Results

Between January 2000 and September 2009, 189 thyroid cancer patients initiated surgical treatment at the Third Surgical Unit. Of these, 65 underwent total thyroidectomy, 34 underwent total thyroidectomy with selective neck dissection, 59 total thyroidectomy with radical or radically modified neck dissection, 15 underwent procedure in order to complete a total thyroidectomy (due to the discovery of occult thyroid cancer in patients with lobectomy for benign tumour), 12 reinterventions to complete thyroidectomy with radical or radically modified neck dissection (of which 8 for lymph node recurrence in less than 2 years), 2 tracheostomies and 2 exploratory cervicotomies.

Of the 189 patients treated for malignant thyroid disease, 138 were papillary thyroid carcinomas (**Figure 2. a, b**), 26 follicular carcinomas (**Figure 3. a, b, c, d**), 12 medullary carcinomas (**Figure 4. a, b**), 8 anaplastic carcinomas (**Figure 5. a, b**), 3 metastases from another cancer localization, and 2 non-Hodgkin's malignant lymphomas (**Figure 6.**).

Table 1. TNM definitions (Bychkov, 2019)

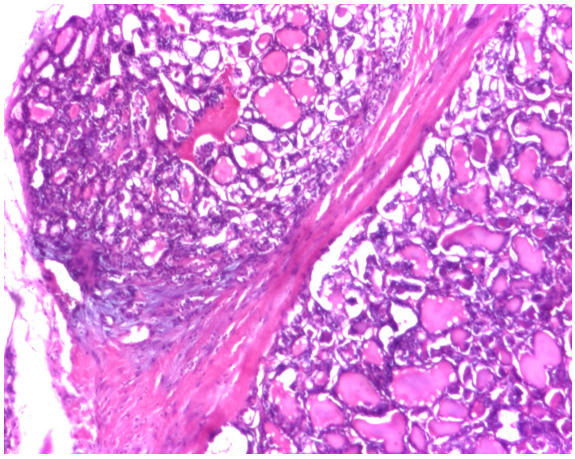
Primary tumor (pT) for papillary, follicular, poorly differentiated, Hürthle cell and anaplastic thyroid carcinomas:	**Regional lymph node (pN):**	**Distant metastasis (M):**
TX: Primary tumor cannot be assessed	**NX:** Regional lymph nodes cannot be assessed	**M0:** No distant metastasis
T0: No evidence of primary tumor	**N0:** No evidence of regional lymph node metastasis	**M1:** Distant metastasis
T1: Tumor ≤ 2 cm in greatest dimension limited to the thyroid	**N0a*:** One or more cytologic or histologically confirmed benign lymph nodes	
T1a: Tumor ≤ 1 cm in greatest dimension limited to the thyroid	**N0b*:** No radiologic or clinical evidence of locoregional lymph node metastasis	
T1b: Tumor > 1 cm but ≤ 2 cm in greatest dimension limited to the thyroid	**N1*:** Metastasis to regional nodes	
T2: Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid	**N1a*:** Metastasis to level VI or VII (pretracheal, paratracheal, prelaryngeal / Delphian or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease	
T3: Tumor > 4 cm limited to the thyroid or gross extrathyroidal extension invading only strap muscles	**N1b*:** Metastasis to unilateral, bilateral or contralateral lateral neck lymph nodes (levels I, II, III, IV or V) or retropharyngeal lymph nodes	
T4: Includes gross extrathyroidal extension into major neck structures		
T4a: Tumour invades subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve		
T4b: Tumour invades prevertebral fascia or carotid artery or mediastinal vessels		
Primary tumor (pT) for medullary thyroid carcinomas:		
TX - T3: *Definitions are similar to the above*		
T4: Advanced disease		
T4a: Moderately advanced disease; tumor of any size with extension into subcutaneous soft tissue, larynx, trachea, esophagus or recurrent laryngeal nerve		
T4b: tumor of any size with extension toward the spine or blood vessels, invading the prevertebral fascia or encasing the carotid artery or mediastinal vessels		

Table 2. AJCC prognostic stage grouping (Bychkov, 2019)

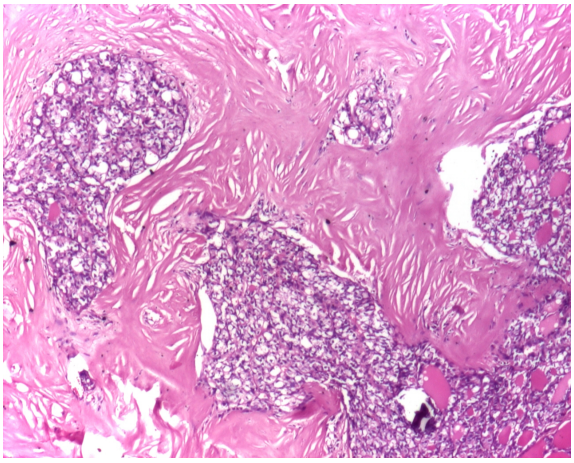
Differentiated thyroid cancer			
Age at diagnosis < 55 years			
Stage I:	any T	any N	M0
Stage II:	any T	any N	M1
Age at diagnosis ≥ 55 years			
Stage I:	T1	N0 / NX	M0
	T2	N0 / NX	M0
Stage II:	T1	N1	M0
	T2	N1	M0
	T3a / T3b	any N	M0
Stage III:	T4a	any N	M0
Stage IVA:	T4b	any N	M0
Stage IVB:	any T	any N	M1
Medullary thyroid cancer:			
Stage I:	T1	N0	M0
Stage II:	T2	N0	M0
	T3	N0	M0
Stage III:	T1 - 3	N1a	M0
Stage IVA:	T4a	any N	M0
	T1 - 3	N1b	M0
Stage IVB:	T4b	any N	M0
Stage IVC:	any T	any N	M1
Anaplastic thyroid cancer:			
Stage IVA:	T1 - T3a	N0 / NX	M0
Stage IVB:	T1 - T3a	N1	M0
	T3b	any N	M0
	T4	any N	M0
Stage IVC:	any T	any N	M1

From the study group, 68 patients were diagnosed in the Endocrinology Clinic with malignant puncture confirmed subsequently by paraffin examination, 106 patients with suspected puncture, which subsequently, through paraffin examination, proved to be thyroid neoplasm and 15 were diagnosed postoperatively in the histopathologically exam to paraffin (patients who had thyroid lobectomy and who subsequently underwent thyroidectomy). Patients with suspicious puncture that were found to be benign for paraffin exams were excluded from the study. There has been a steady increase in the incidence of thyroid carcinoma through a real increase in incidence and probably early diagnosis of this condition.

For papillary thyroid neoplasms the staging is different for those under 55 years of age (stage I any T, any N, M0 and stage II - any T, any N, M1) and over 55 years old (stage I - T1N0M0, stage II - T2N0M0, Stage III T1-3, N1M0, T3N0M0, Stage IV T4N0-1M0, Any T, Any N, M1). For medullary thyroid tumours, the classification is the same as for papillary neoplasms over 55 years, and the anaplasia is considered Stage IV (**Table 2**).

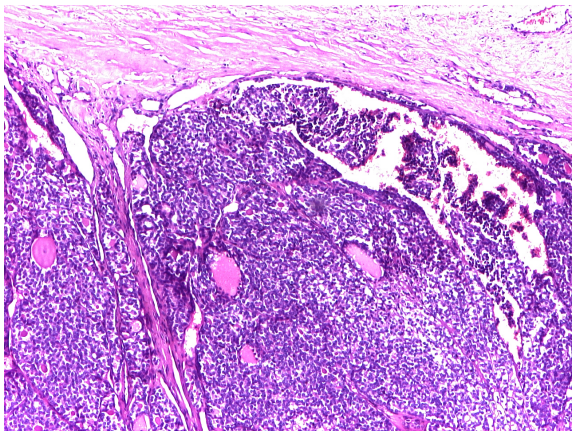


a. Papillary carcinoma, follicular type HE, x 10

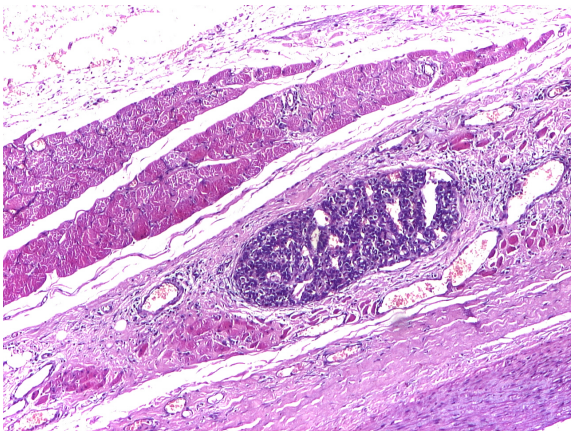


b. Papillary carcinoma, follicular type, HE, x4

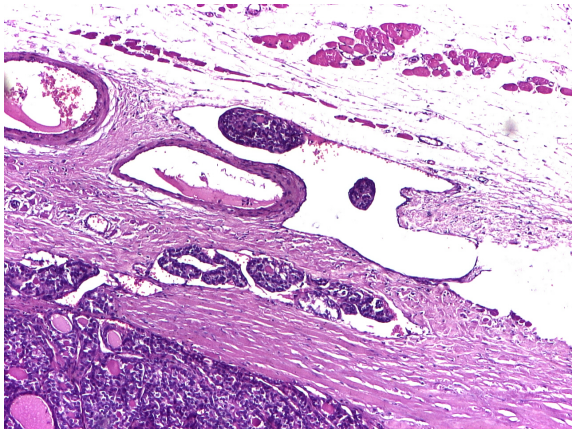
Figure 2. Papillary thyroid carcinomas



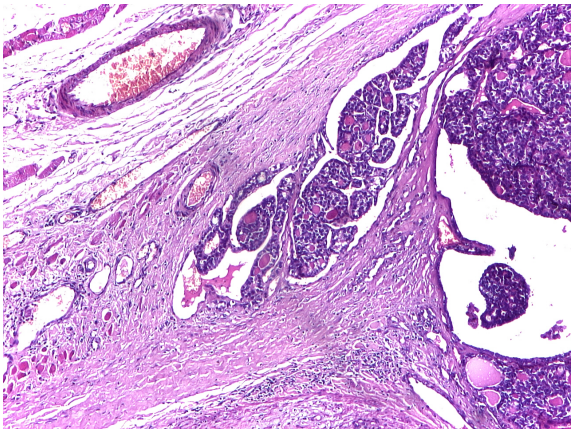
a.. Compact areas and capsular involvement HE, x 4.



b. Capsular tumour embolisms, HE, x 4

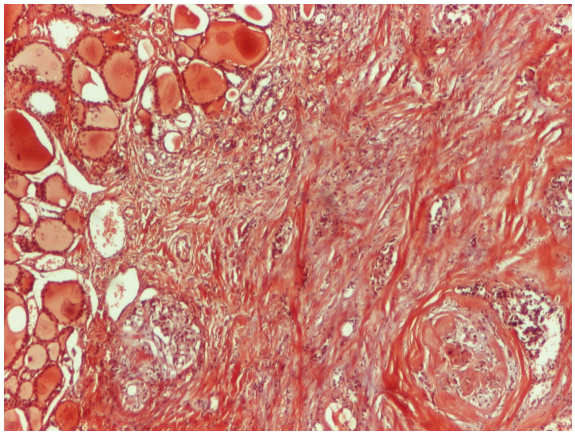


c. Tumour embolism: medium sized capsular vessels, HE, x10

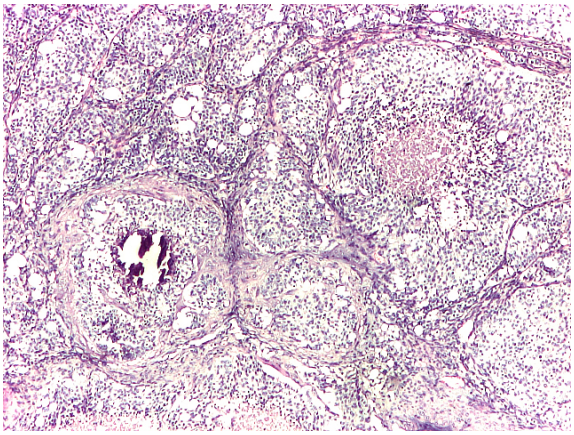


d. Capsular tumour embolisms, HE, x10

Figure 3. Follicular carcinomas

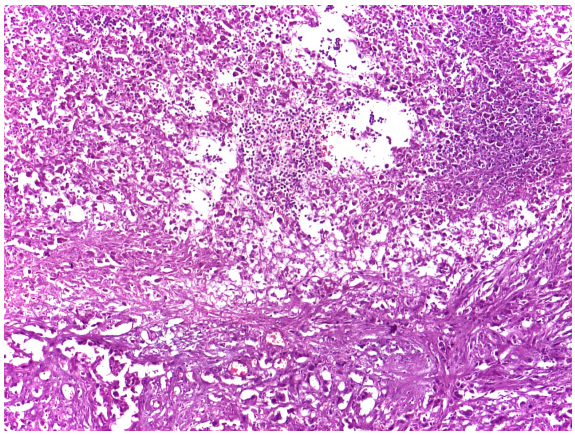


a. Medullary carcinoma, amyloid stroma, Congo red, x10

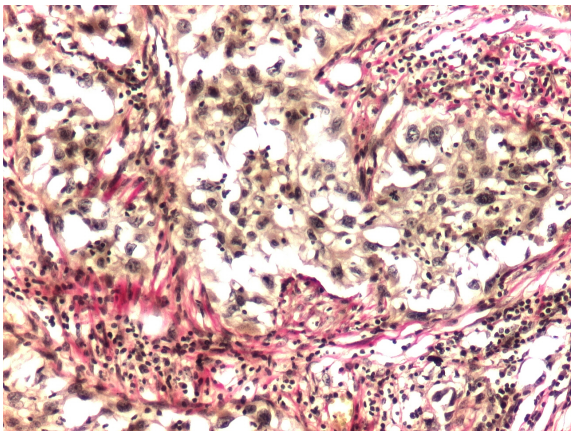


b. Compact tumour proliferation with necrosis and calcification areas, HE, x4

Figure 4. Medullary carcinoma



a. Epithelial areas with massive tumour necrosis, HE, x 4



b. Epithelial areas with marked pleomorphism, VG, x10

Figure 5. Anaplastic carcinomas

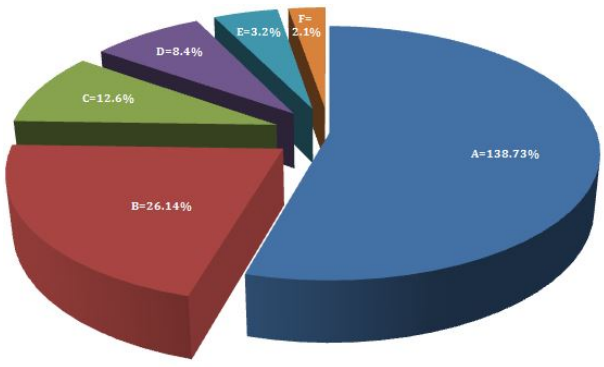


Figure 6. Histologic types of cancer; A=papillar cancer; B=anaplastic cancer; C=follicular cancer; D=thyroid metastases; E=medullar cancer; F=LMNH

91 patients from the study group that underwent surgery were in the following stages:

- 68 patients in stage I (regardless of histological form);
- 72 patients in stage II (regardless of histological form);
- 26 patients in stage III (regardless of histological form);
- 23 patients in stage IV (regardless of histological form) - **figure 7**;

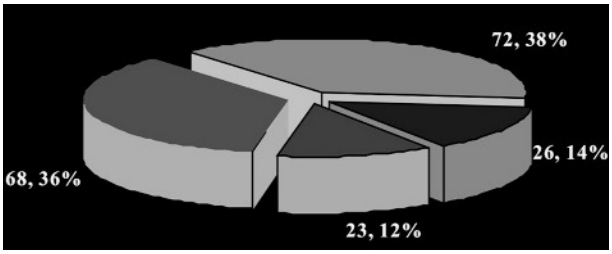


Figura 7. Patients number depending on tumour stage

In the study group, the following surgical interventions were performed: 65 total thyroidectomies plus 34 total thyroidectomies with selective neck dissections (52.38%) for Stage I or II patients, except for medullary thyroid cancer; 59 total thyroidectomies accompanied by radical or radically modified neck dissection (31.21%), for Stage III or IV patients or those with non-medullary thyroid neoplasm at any stage; 2 palliative interventions (tracheostomies) and 2 exploratory cervicotomies in advanced thyroid tumour, surgically outdated (**Figures 8.a., b., c.).**

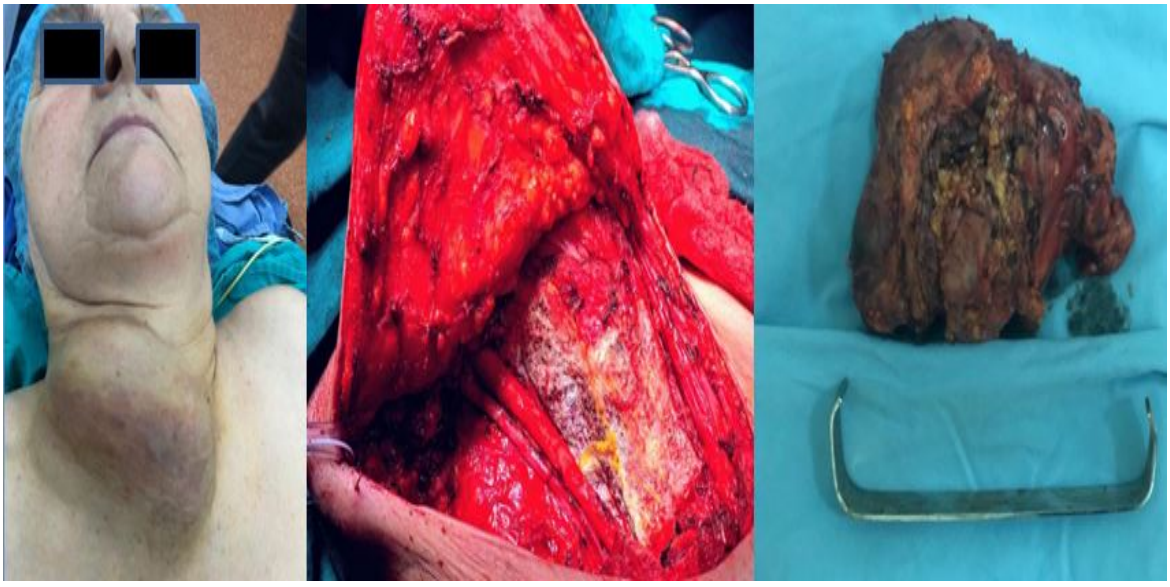


Figure 8.a. T4B Giant tumour after radical neck dissection

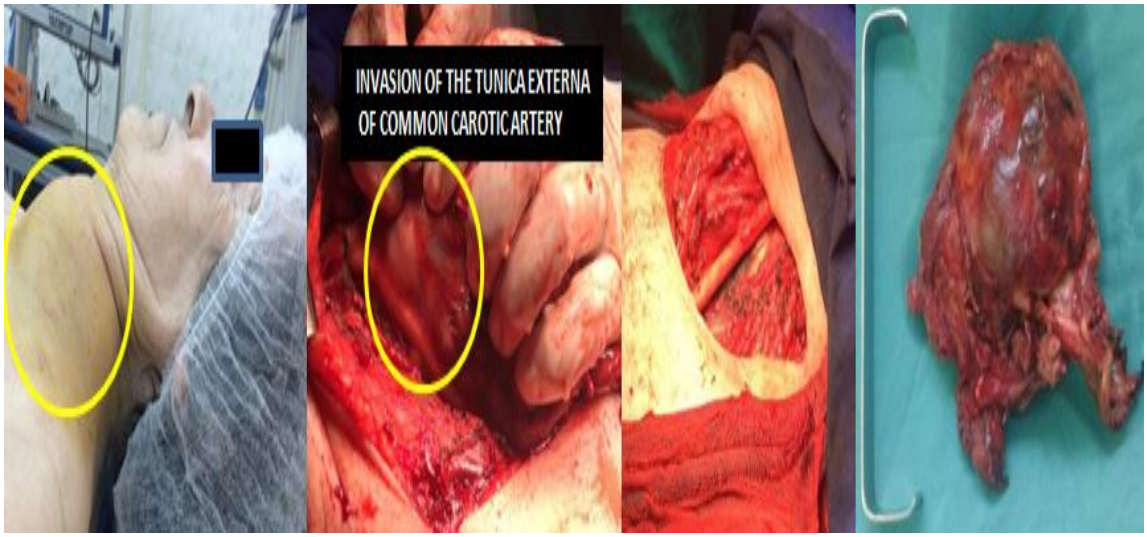


Figure 8.b. Modified radical dissection for thyroid tumour invading common carotid tunica externa artery

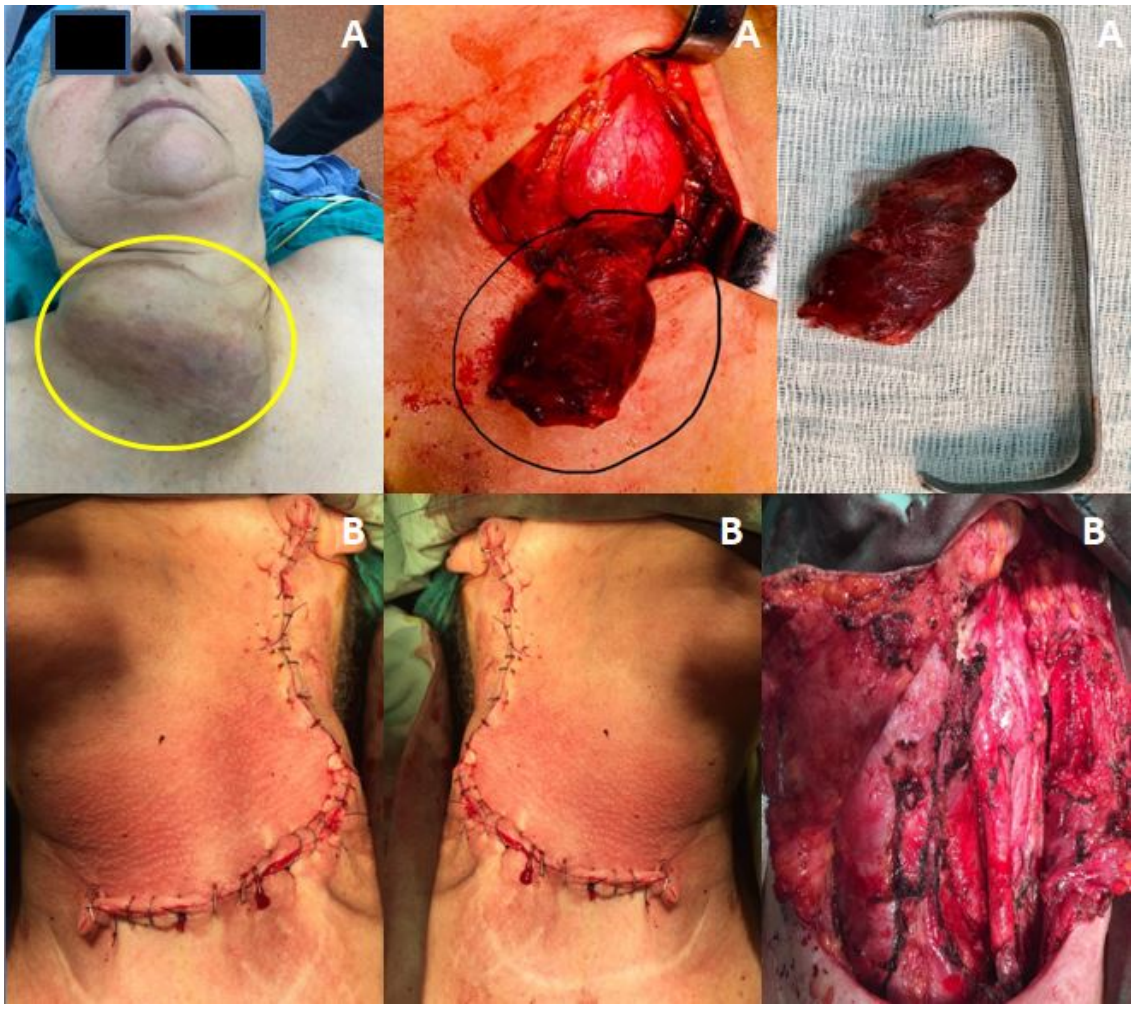


Figure 8.c. A=Giant parathyroid adenoma situated in the superior mediastinum; B=Radical modified extended neck dissection for an extensive tumour.

At the level of the thyroid lodge, extensive formations can occur with extrinsic origin (**Figure 8.d**.).

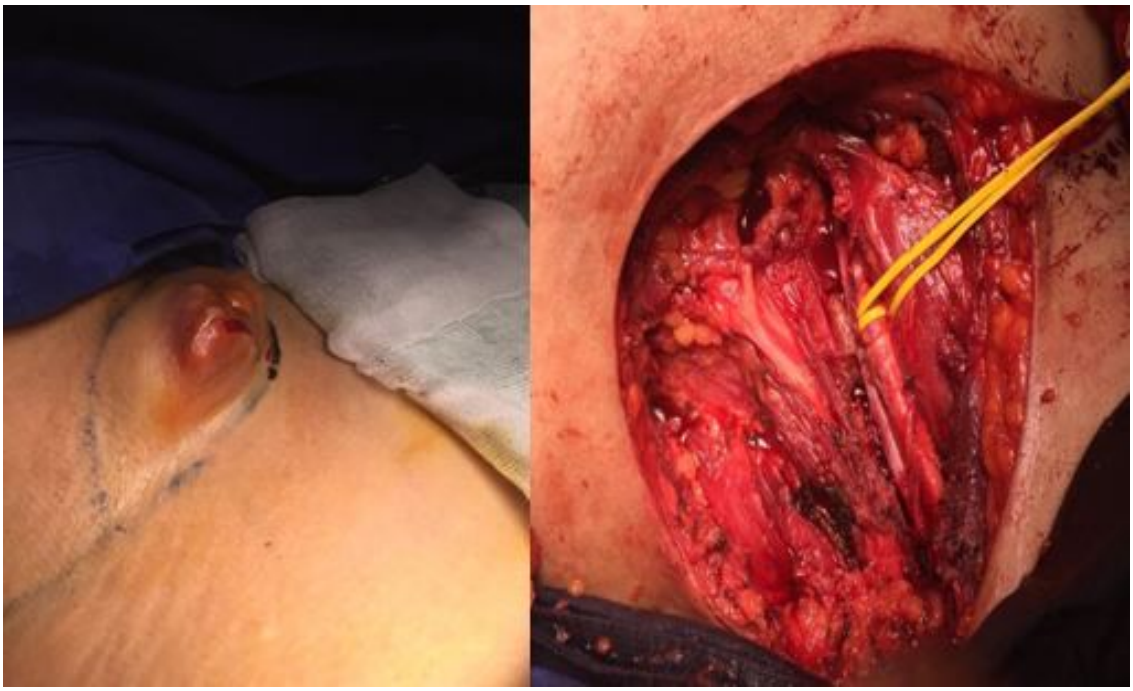


Figure 8.d. Laterocervical metastatic endometrial cancer, 10 years after hysterectomy - modified radical neck dissection

In the 59 patients with radical or radically dissected dissection, the following surgical procedures were performed:

- 29 radical dissections (with internal jugular vein resection, sternocleidomastoidian, spinal nerve accessor and limph nodes removal - levels I-V);
- 30 radically modified dissections (with the preservation of at least one non-lymphatic structure compared to those with radical dissection or the preservation of another anatomical element).

It should be noted that of the 59 patients, 3 had bilateral dissection and two had radically modified dissection in the first stage and secondly (6 or 10 months after the first intervention) radical dissection on the opposite side (**Figure 8.e.**).

One of the patients who required a modified radical dissection of the neck with the approach of the upper mediastinum showed the peculiarity that thyroid tumour had mechanical compression on the superior cave vein. This led to the development of superior cavo-cave collateral circulation at the level of anterolateral thoracic regions (**Figure 9**).

Regarding the immediate postoperative complications, of the 189 surgical patients, there were 6 cases of bleeding (3.17%) (in which the surgery haemostasis was done), 7 (3.70%) cases of unilaterally recurrent nerve damage (patients in stage IV with recurrent nerve invasion), the remaining 176 (93.12%) being without immediate complications.

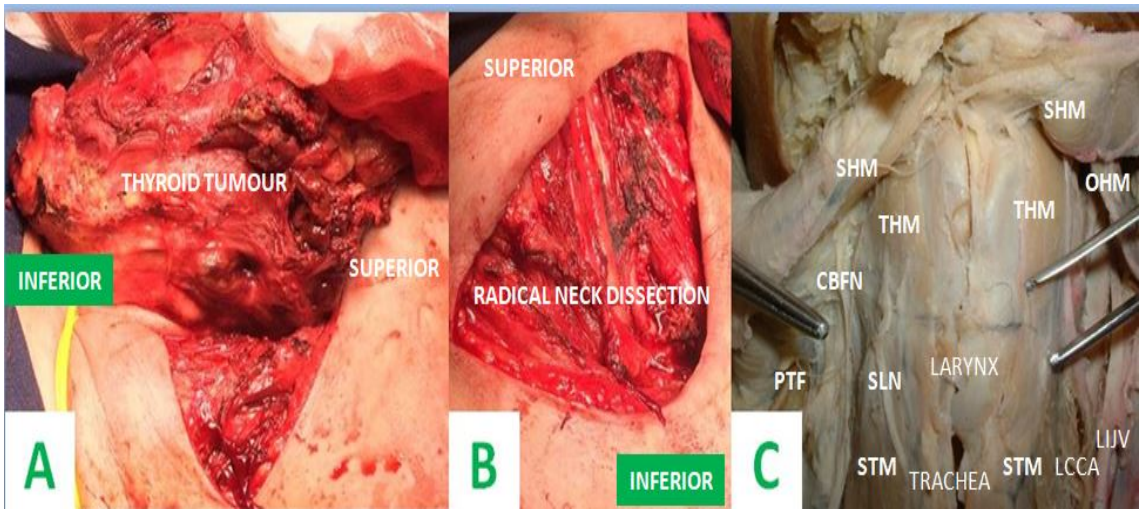


Figure 8.e. Radical neck dissection; A=thyroid tumour excision; B=result of total thyroid ectomy; C=anatomical landmarks of the radical neck dissection area; STM=sternothyroideus muscle; PTF= fascia pretrachealis; LCCA=left common carotic artery; LIJV= left internal jugular vein; SLN=superior laryngeal nerve; THM=thyrohyoideus muscle; OHM=omohyoideus muscle; SHM=sterno-cleido-hyoideus muscle; CBFN=cervical branch of facial nerve

Follow up showed that of the 189 patients, 6 months after surgery, 15 patients (7.93%) had permanent hypoparathyroidism. Also at 24 months there were 8 (4.23%) postoperative recurrences that needed surgery (3 cases at <1 year and 5 cases at> 1 year), all 8 patients being in the group of the 12 thyroid that underwent radical neck dissection after total thyroidectomy in the first stage.

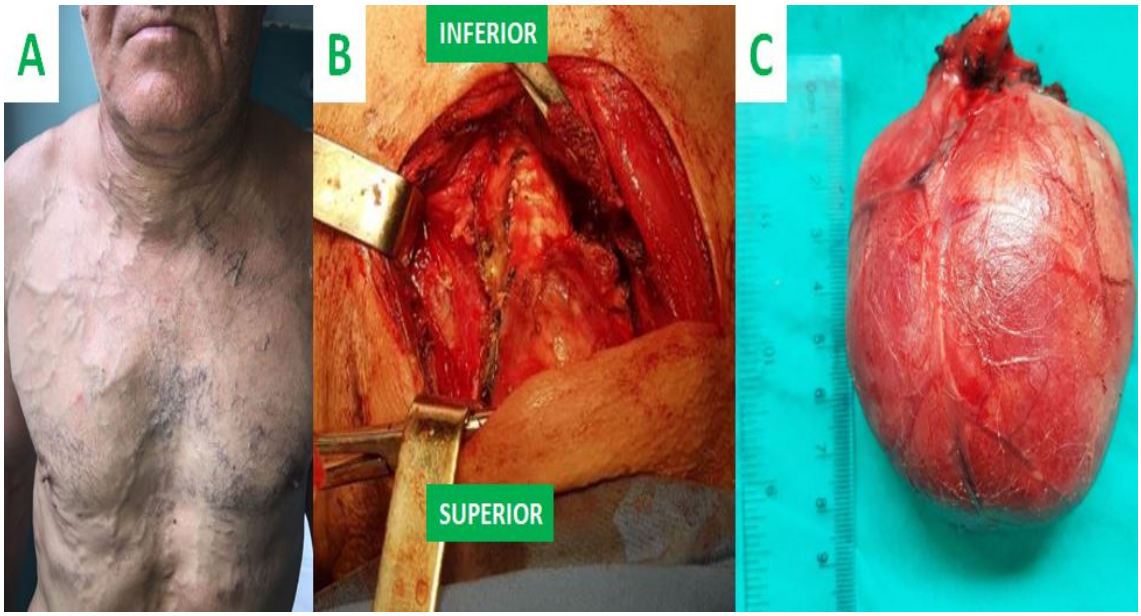


Figure 9. Pacient with thyroid tumour which compresses the superior cava vein; A=superior cavo-cave collateral circulation circulation; B=modified radical neck dissection technique; C=thyroid papillary cervical mediastinal cancer

Thus, relapse for radical neck dissection is 13.55% (5.08% before 1 year and the rest 8.47% after one year). In the 8 patients with relapse, unilateral dissection was performed. In two patients it was performed the controlateral dissection after controlateral lymph node invasion at 6 and 10 months postoperatively.

1.2.4. Discussions

As we mentioned above, radical neck dissection technique was described by George Crile in 1906. This procedure has often been used in the staging of metastatic cancers of the head and neck. The procedure included removal of cervical lymph nodes and sacrificing internal jugular vein, major auricular nerves as well as sternocleidomastoid, digastric and stilohioid muscles. Subsequently, the technique was modified, allowing for the preservation of important cervical anatomical structures (Crile, 1987). Today, the term radical dissection of the neck refers to the functional dissection - Bocca - of the neck (Bocca, 1980).

In turn, the radically modified dissection may be of three types: type I with the maintenance of the spinal accessory nerve, type II with the maintenance of internal jugular vein and / or the spinal accessory nerve and type III with internal jugular vein preservation and / or the accessory spinal nerve and the sternocleidomastoid muscle.

The results evaluation in thyroid cancer surgery is done by assessing the occurrence of tumour recurrence which is the most important prognostic factor.

There is a virtual consensus among surgeons that patients with clinically palpable cervical metastases should undergo neck dissection.

In the 189 patients included in this study we used the Spiro classification from 1994:

1. Radical neck dissection (includes dissection of 4 or 5 ganglion levels):
   - conventional radical dissection;
   - radically modified dissection;
   - extensive radical dissection;
   - radically extensive modified dissection.
2. Selective neck dissection (3levels of lymph node dissection):
   - suprahioid neck dissection;
   - jugular dissection (levels II-IV);
   - dissection of other (any) 3 nodal levels.
3. Limited neck dissection (dissection of less than 2 levels of lymph nodes):
   - paratracheal lymph node dissection;
   - dissection of mediastinal lymph nodes;
   - dissection of other (any) 1 or 2 lymph nodes levels.

The lymph nodes considered in the radical neck dissection are as follows: level I submental and submandibular lymph nodes, level II superior jugular lymph node (anterior, posterior, superior, inferior), level III middle jugular lymph nodes (anterior, posterior, superior, inferior), level IV inferior jugular lymph nodes (anterior, posterior, superior, inferior), level V lymph nodes group of the posterior cervical triangle, level VI pretracheal, paratracheal and precricoid lymph nodes, and level VII superior mediastinal lymph nodes.

Neck dissection plays an essential role in the management of head and neck cancer. The dilemma of approaching the radical neck dissection is that the most differentiated types of thyroid cancer commonly give clinically significant cervical metastases. This phenomenon occurs especially in young patients with papillary thyroid carcinoma (Qu et al., 2019).

One of the indications of modified radical neck dissection in well differentiated thyroid cancer is to establish the topography of cervical lymph adenopathy either by palpation or radiology.

Confirmation of metastatic disease can be achieved by a fine needle preoperative aspiration performed under echographic guidance. Biopsy of the "sentinel" lymph node of the jugular-carotid chain using mapping with methylene blue stains can be a feasible and valuable method for estimating lymphatic status in the neck compartment (Dzodic, 2006).

Prophylactic intervention is recommended for cases of papillary carcinoma demonstrating two or more of the following four features: male gender, age 55 years or older, maximum tumour diameter greater than 3 cm, and extrathyroid massive extension (Ito, 2007).

Recent studies reported the frequent occurrence of metastases in the anterior cervical median (64.1%) and lateral (44.5%) regions (Wada, 2003).

Instead of radical neck dissection, in the past, many surgeons have supported local removals of "picking berry" designed to eliminate coarse lymphadenopathy (Raina, 1983; Nicolosi, 1993).

However, these procedures are associated with a higher rate of local recurrence requiring corrective surgery associated with a higher complication rate (Musacchio, 2003), close to that of radical dissections. The same is true for limited modified neck dissection, where the superior extension of the surgery is limited to the spinal accessor nerve (Pingpank, 2002; Gemsenjäger, 2003; Kupferman, 2004).

In early thyroid cancer (Stage I or II), is sufficient total thyroidectomy with the removal of lymph nodes from the median or lateral neck compartment (selective neck dissection), but this is not recommended in medullary thyroid cancer, when radical neck dissection is indicated regardless of stage (Moley and DeBenedetti, 1999).

In advanced thyroid cancer (stage III or IV) as well as in medullary thyroid cancer total thyroidectomy accompanied by unilateral or bilateral neck dissection is the recommended procedure to improve the recurrence rate (Moley and DeBenedetti, 1999).

The controversy consists in preserving or removing internal jugular veins together with adjacent lymph nodes. Recent studies performed by ultrasonographic evaluation of internal jugular veins allowed the hemodynamic states to be recorded in different patients positions. Their results show that internal jugular vein is not the primary pathway of cerebral venous drainage in sitting position and calm breathing (Gallo, 2013; Chen, 2019).

Generally, young patients with papillary thyroid cancer have a better prognosis than older patients despite their more frequent ganglion metastases. Some studies suggest that radically modified neck dissection (bilateral) can prevent reintervention for lymph nodes recurrence but it does not seem to influence prognosis in young patients (Voutilainen et al., 2001). Both internal jugular veins can be resected, but at least 6 weeks apart.

In contrast, the survival of elderly patients appears to be low in those with recurrent lymph nodes. Thus, elderly patients with risk factors for controlateral lymph nodes

recurrence are the ideal candidates for radically modified bilateral dissection (Ohshima et al., 2000).

Although used, it seems that selective neck dissection leads to increased recurrence, making it an inefficient technique for advanced thyroid cancer (especially non-papillary cancer). However, there are other studies demonstrating that this technique is safe enough to prevent recurrence.

The incidence of chronic neuropathic pain after neck dissections is approximately 40%. Due to its location, the superficial cervical plexus occupies an anatomic position that exposes it to the risk of structural changes (fibrosis, withdrawal phenomena associated with radiotherapy or neuroma formation) posttiroidectomy. Standard drug therapy in these patients includes pharmacological treatments due to neuropathic pain (gabapentinoids, tricyclic antidepressants). Modern techniques of pain therapy with invasive ultrasound allow for the successful treatment of these postoperative complications by pulse radiofrequency ablation of nerve structures (Valls, 2019).

To minimize surgical morbidity and neck scarring, minimally invasive thyroididectomy and endoscopic robotic thyroidectomy have developed in the last 20 years. They use the cervical, axillary, anterior thoracic, mammar or postauricular approach. Of these, the transaxillary gas-free approach, the bilateral axillary-mammary approach, the post-auricular approach of facial lifting, and the transoral vestibular approach are currently in use. The main advantage of endoscopic thyroididectomy is the cosmetic, while the rate of complications is similar to that of conventionally operated patients and requires a team of experienced surgeons. Operating time is significantly higher in this case (Berber, 2016; Tae, 2019).

Modern radiological techniques allow a precise identification of the lymph nodes involved in the paraneoplastic process, the nodal compartments of the neck and even their mapping. This allows for dissection to be oriented to lymph nodes compartment (or selective) instead of the extended one, but requires close cooperation between an experienced radiologist and the operative team. There are evidences that proove this more conservative strategy allows local control of the disease, while morbidity is minimized. A better cosmetic result is also obtained (Fama, 2015; Sakofaras, 2019).

1.2.5. Conclusions

Thus, the radical neck dissection in advanced thyroid cancer, although a complex surgical technique, with possible incidents and postoperative complications, is the primary therapeutic solution in advanced thyroid cancers with long-term good results in a specialized surgery center.

1.3. POST-THYROIDECTOMY SCARS – FOLLOW UP AND MANAGEMENT

1.3.1. Introduction

Incisions, burns, acne, trauma and other wounds are associated with a natural healing process that lead to scar formation. This process is accompanied with physical, aesthetic, psychological and social consequences (Monstrey et al., 2014).

Itching (Van Loey et al., 2008; Willebrand et al., 2004), stiffness, scar contractures, tenderness and pain are physical symptoms which manifest with the healing process. The visible scars often lead to significant cosmetic problems, psychological stress (Bakker et al., 2013) and loss of selfesteem (Robert et al., 1999). Keloid and hypertrophic scars impaired quality of life (QoL) in same extent as serious dermatologic conditions.

Dermatology Life Quality Index (DLQI) is a validated dermatology specific QoL indicator. DLQI was quantified as being 7.79 for keloid and hypertrophic scars (Balci et al., 2009), 8.15 for vitiligo (Dolatshahi et al., 2008), 8.80 for severe atopic dermatitis (Misery et al., 2007) and psoriasis (Mazzotti et al., 2005), 10.09 for scabies (Jin-gang et al., 2010). Visible scars have a greater impact on QoL, for example the DLQI for post-thyroidectomy scars was quantified as being 9.02 (Choi et al, 2014). Silicones are the gold standard therapy in scar management, being enough supported by clinical trials that offer evidence-based recommendations (Monstrey et al., 2014).

Silicones are a non-invasive preventive and therapeutic measure. The main mechanism of action of silicon sheets or silicone gels is the hydrophobic occlusion and a consecutive underneath increase of hydration and decrease of trans-epidermal water loss (TEWL). TEWL cause a dehydration of dermal layers. Stimulation of keratinocytes in order to synthesize pro-fibrotic signals is a response of dehydration. Pro-fibrotic signals stimulate fibroblasts to produce excessive dermal collagen in order to obstruct the space which allows TEWL (Mustoe et al., 2008).

A reduction of angiogenesis and capillary perfusion is a beneficial consequence of hydration and occlusion which explains the efficacy of silicones in scar management. Additional mechanisms of action are: increasing of collagenase activity due to increasing of the skin surface temperature (Musgrave et al., 2002) and a realignment of collagen due to negatively charged static electric determined by friction between silicone gel and the skin surface (Medhi et al., 2013).

The present study assessed the efficacy and safety of REGEN-SIL® gel in therapeutic management of post-operative hypertrophic and keloid scars. REGEN-SIL® is a complex silicone-based product which contains 4 types of silicones: high and low molecular dimethicone, trimethylsiloxisilicate and dimethicone cross polymer. The balanced composition leads to a unique silicon product with excellent adhesive long lasting, wash off resistance that forms a highly hydrophobic barrier, but permeable for gases exchange. REGEN-SIL® was compared with another silicone-based product which contains siloxane, polydimethylsiloxane and alkyl methyl silicone.

As siliconic products have diverse compositions, there is a high relevance to comparatively investigate the clinical efficacy of the different formulations. Few studies have evaluated the comparative efficacy of available products on the pharmaceutical market. Consequently, a prospective, comparative, randomized, open study has been conducted in order to assess the efficacy and safety of two products authorised as medical devices with the same therapeutic indications.

1.3.2. Materials and methods

1.3.2.1. *Study group*

One hundred patients undergoing surgical incisions in the anterolateral cervical region for thyroid and parathyroid glands were evaluated for inclusion in study between June, 2015 and March, 2016. Participant inclusion criteria were as follows: patients with age between 18 and 75 years, regardless of sex, with sutured wounds after incisions from surgery for thyroid and parathyroid glands approach, patients with closed wounds without complications (infections), patients which signed the informed consent.

Exclusion criteria were as follows: patients that did not sign the informed consent, allergies to silicone, patients with open or infected wounds, patients who follow other treatments for therapeutic management of scar (topical corticosteroids, intralesional corticosteroids, and/or 5-fluorouracil or other therapeutic options for scar management).

All patients were randomly assigned in one of the two arms of the study: REGEN-SIL® gel or another silicone gel - Strataderm® (Stratpharma AG CH-4051, Basel, Switzerland) available on pharmaceutical market authorized for the same therapeutic indications.

The arms were categorized as REGEN-SIL® group (50 patients) and Silicone Gel group (50 patients), respectively. Patients were instructed to use the product according to approved information: 1 application/day in a thin layer. If the area with scar was washed, the administration was repeated, in order to create a permanent contact of the product with the scar. The application of both silicone-based products started immediately after the sutures were removed.

1.3.2.2. *Evaluation criteria and outcome measures*

Efficacy assessment.

At the initial point, the patients' scars were photographed and evaluated using the Vancouver Scar Scale (VSS) (Kim et al., 2014): pigmentation, vascularity, height, pliability, pain, and itchiness being measured (**Table 3**). The afore mentioned evaluation was performed by dermatologists; photos and evaluation through VSS being repeated after one month and three months of treatment. The scarring process depending on age was comparatively assessed taking into account the VSS score for patients < 60 years and ≥ 60 years in both treatment groups.

Table 3. Vancouver Scar Scale (VSS) score after Kim et al., 2014

Feature		Score
Pigmentation	Normal	0
	Hypopigmentation	1
	Mixed pigmentation	2
	Hyperpigmentation	3
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Height	Normal	0
	<2mm	1
	2-5mm	2
	>5mm	3
Pliability	Normal	0
	Supple (flexible with minimal resistance)	1
	Yielding (giving way to pressure)	2
	Firm (inflexible, not easily moved, resistant to manual pressure)	3
	Banding (rope-like tissue that blancheswith extension of the scar)	4
	Contracture (permanent shortening of scar, producing deformity or distortion)	5
Pain	None	0
	Occasional	1
	Requires medication	2
Itchiness	None	0
	Occasional	1
	Requires Medication	2

Safety assessment.

Side effects that could occur following administration of both products have been monitored.

1.3.2.3. *Patient and physician satisfaction*

The satisfaction level was evaluated according to a 5 points scale (1–weak,2–moderate, 3–good, 4– very good, 5 – excellent) by both the patients and physicians, at one month and three months after treatment onset.

Statistical analysis

Descriptive statistics were used for demographic data. Z-test two samples for means was used to compare values between baseline and subsequent visits (within the group analysis) and between treatment groups at subsequent visits (intergroup analysis). A p value less than 0.05 was considered statistically significant.

1.3.2.4. *Approval and ethics statement*

Both products are registered as medical devices and in this clinical study were used

according to the information for users. The scientific research was thus conducted after a non-interventional design and no approval from national regulatory authority being requested.

This study was approved by the Ethics Committee of "Sfântul Spiridon" Emergency County Hospital, Iași, Romania. All patients were informed about the study details and signed the informed consent.

1.3.2.5. *Baseline and clinical characteristics of the patients*

This study enrolled one hundred patients, but only ninety-three patients finished the trial; the exclusion reasons from the study of the 7 patients arepresented in **Table 4**. All participants were female with a mean age of 50.4 years (total range 22 - 75 years, (**Table 5).**

All patients underwent incisions in the anterolateral cervical region for thyroid and parathyroid glands surgical approach (**Table 6**).

Table 4. Exclusion reasons of patients from initial lot

Exclusion reasons	Number of patients		
	REGEN-SIL® group	Sillicone Gel group	Total
Dropping out for personal reasons	2	3	5
Using of both products	1	-	1
Development of post-operative ecchymosis in surgical incision area, independently from topical application of product	1	-	1
Total excluded patients	4	3	7
Patients that completed the study	46	47	93

Table 5. Demographic characteristics of both groups

Demographic characteristics	**REGEN-SIL® group (n=46)**	**Sillicone Gel group (n=47)**	**Total**
Age			
Mean ± SD, years	53.6 ± 11.6	47 ± 11	50.4±11.7
[min, max], years	[25-75]	[22-70]	[22-75]
Sex			
F/M, n	46/0	47/0	93/0

F – female, M – male, max – maximum, min – minimum, n – number of patients, SD – standar deviation

After sutures were removed, no significant differences were observed between groups regarding VSS scores at baseline (**Table 7**).

The practiced surgical technique was the horizontal incision in anterolateral cervical region, with 7 cm length, at 2 cm cranial to the sternal manubrium and closure.

Suture was carried out with heavy resorbable vicryl 30 for median raphe of infrahyoid muscles (strap muscles), heavy absorbable suturefor subcutaneous, fast absorbable suture 30 for separate suture intradermal, Steri-strip of 5 mm on the whole length of the wound.

Table 6. Surgical interventions

Surgical interventions	REGEN-SIL® group (n=46)	Sillicone Gel group (n=47)	Total
Benign total thyroidectomy	42	44	86
Malignant total thyroidectomy	1	2	3
Benign right thyroid lobectomy	-	1	1
Malignant total thyroidectomy and selective neck dissection (central and 3rd sectors)	1	-	1
Benign total thyroidectomy, subtotal parathyroidectomy	1	-	1
Total	46	47	93

Table 7. Vancouver Scar Scale (VSS) scores at baseline

Score		Baseline Mean ± SD	Intergroup statistical significance (p, α= 0.05)
Pigmentation	REGEN-SIL® group (n=46)	1.89 ± 0.31	NS (p=0.779)
	Sillicone Gel group (n=47)	1.87 ± 0.34	
Vascularity	REGEN-SIL® group (n=46)	2.48 ± 0.50	NS (p=0.475)
	Sillicone Gel group (n=47)	2.40 ± 0.50	
Height	REGEN-SIL® group (n=46)	2.28 ± 0.45	NS (p=0.247)
	Sillicone Gel group (n=47)	2.17 ± 0.48	
Pliability	REGEN-SIL® group (n=46)	2.04 ± 0.36	NS (p=0.602)
	Sillicone Gel group (n=47)	2.08 ± 0.41	
Pain	REGEN-SIL® group (n=46)	0.93 ± 0.25	NS (p=0.299)
	Sillicone Gel group (n=47)	0.98 ± 0.15	
Itchiness	REGEN-SIL® group (n=46)	0.87 ± 0.34	NS (p=0.130)
	Sillicone Gel group (n=47)	0.96 ± 0.20	
Total VSS	REGEN-SIL® group (n=46)	10.5 ± 2.23	-
	Sillicone Gel group (n=47)	10.47 ± 2.07	

N – number of patients, NS – not statistically significant, SD – standard deviation

1.3.3. Results

1.3.3.1. *Efficacy assessment*

Changes from baseline at 1 month after treatment onset Intragroup analysis. At 1 month after treatment onset, a decrease of vascularity (-24.59%, $p < 0.001$), height (-11.40%, $p < 0.001$) and itchiness (-19.54%, $p = 0.041$) score was recorded for REGEN-SIL® group compared to baseline. These differences reached statistical significance. No significant

differences were observed for pigmentation, pliability and paincompared with baseline in REGEN-SIL® group (Table VI). Total VSS score decreased by 11.61% in REGEN-SIL® group, compared with baseline, after 1 month from treatment onset.

Intergroup analysis.

Pigmentation, height, pliability and pain score differed insignificantly between groups. Vascularity and itchiness scores turned out to decrease significantly in REGEN-SIL® group compared to Silicone Gel group: -8.33% ($p = 0.008$) and -19.54%($p = 0.036$), respectively after 1 month. The differencein terms of total VSS score was also in favour of REGEN-SIL® treatment (-4.52% compared withSilicone Gel group), after 1 month from treatmentonset (**Table 8**).

1.3.3.2. *Changes from baseline at 3 months after treatment onset*

Intragroup analysis. At 3 months after treatment onset, a significant decrease for all parameters of VSS score was recorded compared to baseline in REGEN-SIL® group: pigmentation (-71.46%, $p < 0.001$), vascularity (-70.16%, $p < 0.001$), height (-70.61%, $p < 0.001$), pliability (-62.74%, $p < 0.001$) pain (-41.93%, $p < 0.001$), itchiness (-29.88%, $p = 0.003$). Total VSS score decreased by 63.23% compared with baseline in REGEN-SIL® group (**Table 9**).

1.3.3.3. *Intergroup analysis*.

With the exception of the itchiness score, as shown in **Table 10**, significant differences were recorded between groups at 3 months after treatment onset.

Administration of REGEN-SIL® proved a significant decrease in VSS for REGEN-SIL® group compared with Silicone Gel group in pigmentation (-31.65%, $p = 0.01$), vascularity (-27.45%, $p = 0.001$), height (-28.72%, $p = 0.003$), pliability (-24%, $p < 0.001$), pain (-33.33%, $p = 0.005$).

The difference in terms of total VSS score was maintained after 3 months in favour of REGEN-SIL® treatment (-26.7% compared to total VSS in Silicone Gel group, after 3 months).

Overall, significant reduction of VSS score were observed with the use of REGEN-SIL®. Evolution of VSS scores are also represented in **Figure 10**.

In order to assess the efficacy differences between REGEN-SIL® and Silicone Gel, the percentage of patients with clinical normalized parameters (0score), after 3 months of treatment were represented (**Figure 11**).

1.3.3.4. *Age depending scarring assessment*

Intragroup analysis.

No significant statistical difference was registered between patients younger than 60 years and patients older than 60 years, after 1 month and 3 months, for patients treated with REGEN- SIL® or patients treated with Silicone Gel (except for pliability score with statistically significant difference in Silicone Gel group, after 1 month) (**Table 10**).

Table 8. The values recorded for clinical parameters evaluated at 1 month after treatment onset

Score		Baseline	After 1 month (1st follow-up)				
		Mean ± SD	INTRAGROUP			INTERGROUP	
			Mean ± SD	%compared to initial	Statistical significance (p,α= 0.05)	%intergroup difference	Statistical significance (p,α= 0.05)
Pigmentation	REGEN-SIL® group (n=46)	1.89 ± 0.31	1.78 ± 0.42	-5.82%	NS	-1.65%	NS (p= 0.76)
	Sillicone Gel group (n=47)	1.87 ± 0.34	1.81 ± 0.40	-3.20%	NS		
Vascularity	REGEN-SIL® group (n=46)	2.48 ± 0.50	1.87 ± 0.34	-24.59%	S, p<0.001	-8.33%	S, p = 0.008
	Sillicone Gel group (n=47)	2.40 ± 0.50	2.04 ± 0.29	-15%	S, p<0.001		
Height	REGEN-SIL® group (n=46)	2.28 ± 0.45	2.02 ± 0.15	-11.40%	S, p<0.001	-4.82%	NS (p= 0.15)
	Sillicone Gel group (n=47)	2.17 ± 0.48	2.11±0.37	-2.76%	NS		
Pliability	REGEN-SIL® group (n=46)	2.04 ± 0.36	2.02 ± 0.15	-0.98%	NS	1.98%	NS (p= 0.44)
	Sillicone Gel group (n=47)	2.08 ± 0.41	1.98 ± 0.15	-5.10%	NS		
Pain	REGEN-SIL® group (n=46)	0.93 ± 0.25	0.89 ±0.31	-4.30%	NS	2.19%	NS (p= 0.62)
	Sillicone Gel group (n=47)	0.98 ± 0.15	0.91±0.29	- 7.13%	NS		
Itchiness	REGEN-SIL® group (n=46)	0.87 ± 0.34	0.70 ± 0.46	-19.54%	S, p = 0.041	-19.54%	S, p = 0.036
	Sillicone Gel group (n=47)	0.96 ± 0.20	0.87 ± 0.34	-9.37%	NS		
Total VSS	REGEN-SIL® group (n=46)	10.5 ± 2.23	9.28 ± 1.83	-11.61%	-	-4.52%	-
	Sillicone Gel group (n=47)	10.47 ± 2.07	9.72 ± 1.83	-7.07%	-		

N – number of patients, NS – not statistically significant, S – statitically significat, SD – standard deviation

Table 9. The values recorded for clinical parameters evaluated at 3 months after treatment onset.

Score		Baseline	After 3 month (2nd follow-up)				
		Mean ± SD	INTRAGROUP			INTERGROUP	
			Mean ± SD	%compared to initial	Statistical significance (p,α= 0.05)	%intergroup difference	Statistical significance (p,α= 0.05)
Pigmentation	REGEN-SIL® group (n=46)	1.89 ± 0.31	0.54 ± 0.50	-71.46%	S, p<0.001	-31.65 %	S, p = 0.01
	Sillicone Gel group (n=47)	1.87 ± 0.34	0.79 ± 0.41	-57.75%	S, p<0.001		
Vascularity	REGEN-SIL® group (n=46)	2.48 ± 0.50	0.74 ± 0.44	-70.16%	S, p<0.001	-27.45 %	S, p = 0.001
	Sillicone Gel group (n=47)	2.40 ± 0.50	1.02 ± 0.39	-57.50%	S, p<0.001		
Height	REGEN-SIL® group (n=46)	2.28 ± 0.45	0.67 ± 0.47	-70.61%	S, p<0.001	-28.72 %	S, p = 0.003
	Sillicone Gel group (n=47)	2.17 ± 0.48	0.94±0.38	-56.68%	S, p<0.001		
Pliability	REGEN-SIL® group (n=46)	2.04 ± 0.36	2.76 ± 0.43	-62.74%	S, p<0.001	-24%	S, p <0.001
	Sillicone Gel group (n=47)	2.08 ± 0.41	1.00 ± 0.36	-51.92%	S, p<0.001		
Pain	REGEN-SIL® group (n=46)	0.93 ± 0.25	0.54 ±0.50	-41.93%	S, p<0.001	-33.33 %	S, p = 0.005
	Sillicone Gel group (n=47)	0.98 ± 0.15	0.81±0.40	- 17.34%	S, p=0.006		
Itchiness	REGEN-SIL® group (n=46)	0.87 ± 0.34	0.61 ± 0.49	-29.88%	S, p = 0.003	-15.27 %	NS, p = 0.24
	Sillicone Gel group (n=47)	0.96 ± 0.20	0.72 ± 0.45	-25%	S, p=0.001		
Total VSS	REGEN-SIL® group (n=46)	10.5 ± 2.23	3.86 ± 2.85	-63.23%	-	-26.70 %	-
	Sillicone Gel group (n=47)	10.47 ± 2.07	5.28 ± 2.40	-49.57%	-		

N – number of patients, NS – not statistically significant, S – statitically significat, SD – standard deviation

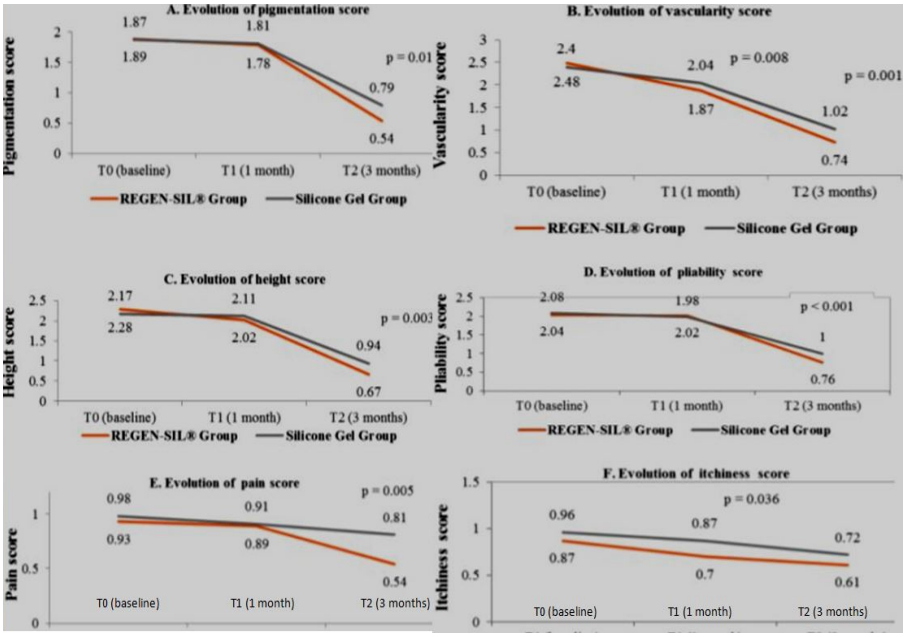


Figure 10. Evolution of VSS scores (statistically significant at $p < 0.05$ within intergroup)

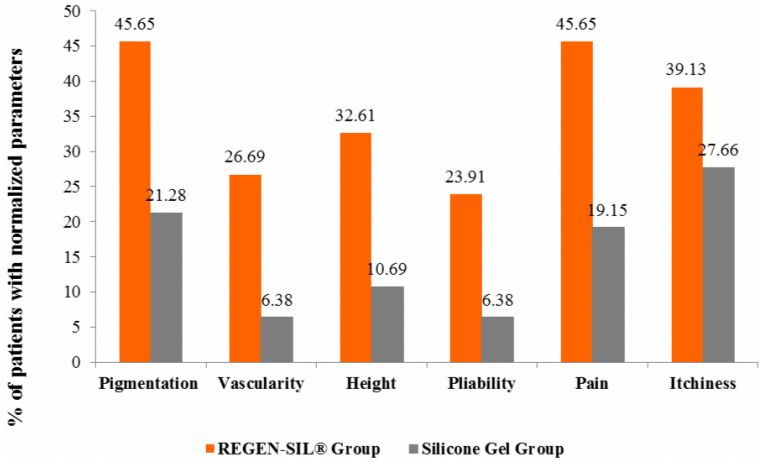


Figure 11. Normalization of clinical parameters after 3 months of treatment

Patients younger than 60 years - Intergroup analysis. Vascularity turned out to decrease significantly in REGEN-SIL® group compared to Silicone Gel group in patients younger than 60 years after 1 month treatment onset. With the exception of the pigmentation and itchiness score, as shown in **Table 11 and Figure 12**, significant differences were recorded between groups, in patients younger than 60 years, at 3 months after treatment onset.

The administration of REGEN-SIL® proved a significant decrease in VSS compared with Silicone Gel group: vascularity (-25%, $p = 0.01$), height (-32.63%, $p < 0.01$), pliability (-16.84%, $p < 0.01$), pain (-31.33%, $p = 0.01$) (**Table 11**). The difference in terms of total VSS score was maintained after 3 months in favour of REGEN-SIL® treatment (- 26.49% compared to total VSS in Silicone Gel group) for patients younger than 60 years.

Patients older than 60 years - Intergroup analysis.

Table 10. The values recorded for clinical parameters depending on age – intragroup analysis

		Pigmentation	Vascularity	Height	Pliability	Pain	Itchiness	Total VSS
REGEN-SIL® group								
After 1 month								
Intragroup	<60 years, mean ± SD	1.82 ± 0.39	1.82 ± 0.39	2.04 ± 0.19	2.04 ± 0.19	0.93 ± 0.26	0.71 ± 0.46	9.36 ± 2,80
	>60 years, mean ± SD	1.72 ± 0.46	1.94 ± 0.24	2.00 ± 0.00	2.00 ± 0.00	0.83 ± 0.38	0.67 ± 0.49	9.16 ± 1.57
	%intragroup difference	5.81%	-6.19%	2.00%	2.00%	12.05 %	5.97%	2.18%
	Statistical significance (p,α= 0.05	NS (p=0.45)	NS (p=0.37)	NS (p=0.42)	NS (p=0.42)	NS (p=0.36)	NS (p=0.74)	-
After 3 months								
Intragroup	<60 years, mean ± SD	0.50 ± 0.51	0.75 ± 0.44	0.64 ± 0.49	0.79 ± 0.42	0.57 ± 0.50	0.54 ± 0.51	3.79 ± 2.89
	>60 years, mean ± SD	0.61 ± 0.50	0.72 ± 0.46	0.72 ± 0.46	0.72 ± 0.46	0.50 ± 0.51	0.72 ± 0.46	3.99 ± 2.85
	%intragroup difference	18.03%	-4.17%	11.11%	-9.72	-14.00 %	25.00%	+5.27 %
	Statistical significance (p,α= 0.05	NS (p=0.47)	NS (p=0.78)	NS (p=0.58)	NS (p=0.63)	NS (p=0.64)	NS (p=0.25)	-
Sillicone Gel group								
After 1 month								
Intragroup	<60 years, mean ± SD	1.83 ± 0.38	2.03 ± 0.28	2.10 ± 0.38	2.29 ± 0.49	0.90 ±0.30	0.85 ± 0.36	10.0 ± 2.19
	>60 years, mean ± SD	1.71 ± 0.49	2.14 ± 0.38	2.14 ± 0.38	2.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	9.99 ± 1.25
	%intragroup difference	7.65%	-12.28%	-1.87%	-14.50%	-10.00 %	-15.00%	+0.1 %
	Statistical significance (p,α= 0.05	NS (p=0.57)	NS (p=0.43)	NS (p=0.78)	S (p<0.01)	NS (p=0.10)	NS (p=0.01)	
After 3 month								
Intragroup	<60 years, mean ± SD	0.68 ± 0.47	1.00 ± 0.39	0.95 ± 0.39	0.95 ± 0.32	0.83 ± 0.38	0.75 ± 0.44	5.16 ± 2.39
	>60 years, mean ± SD	0.86 ± 0.38	1.14 ± 0.38	0.86 ± 0.38	1.29 ± 0.49	0.71 ± 0.49	0.57 ± 0.53	5.43 ± 2.65
	%intragroup difference	-20.93%	-12.28%	10.47%	-26.36%	16.90 %	31.58%	+5.23
	Statistical significance (p,α= 0.05	NS (p=0.35)	NS (p=0.35)	NS (p=0.55)	NS (p=0.08)	NS (p=0.61)	NS (p=0.41)	

N – number of patients, NS – not statistically significant, S – statitically significat, SD – standard deviation

The itchiness score turned out to decrease significantly in REGEN-SIL® group compared to Silicone Gel group in patients older than 60 years, after 1 month treatment onset.

Table 11. The values recorded for clinical parameters depending on age – intergroup analysis

		Pigmentation	Vascularity	Height	Pliability	Pain	Itchiness	Total VSS
<60 years								
After 1 month								
Intragroup	**REGEN-SIL® group** mean ± SD	1.82 ± 0.39	1.82 ± 0.39	2.04 ± 0.19	2.04 ± 0.19	0.93 ± 0.26	0.71 ± 0.46	9.36 ± 2,80
	Sillicone Gel group, mean ± SD	1.83 ± 0.38	2.03 ± 0.28	2.10 ± 0.38	2.29 ± 0.49	0.90 ±0.30	0.85 ± 0.36	10.0 ± 2.19
	%intergroup difference	-0.55%	-10.34%	-2.86%	+10.91%	3.23%	-16.47%	6.83%
	Statistical significance (p,α= 0.05	NS (p=0.97)	S (p=0.02)	NS (p=0.36)	NS (p=0.19)	NS (p=0.68)	NS (p=0.19)	-
After 3 months								
Intragroup	**REGEN-SIL® group**, mean ± SD	0.50 ± 0.51	0.75 ± 0.44	0.64 ± 0.49	0.79 ± 0.42	0.57 ± 0.50	0.54 ± 0.51	3.79 ± 2.89
	Sillicone Gel group, mean ± SD	0.68 ± 0.47	1.00 ± 0.39	0.95 ± 0.39	0.95 ± 0.32	0.83 ± 0.38	0.75 ± 0.44	5.16 ± 2.39
	%intragroup difference	-26.47%	-25%	-32.63%	-16.84%	-31.33 %	-28%	-26.49 %
	Statistical significance (p,α= 0.05	NS (p=0.1)	S (p=0.78)	S (p<0.01)	S (p<0.01	S (p<0.01	NS (p=0.07)	-
>60 years								
After 1 month								
Intragroup	**REGEN-SIL® group, mean** ± SD	1.72 ± 0.46	1.94 ± 0.24	2.00 ± 0.00	2.00 ± 0.00	0.83 ± 0.38	0.67 ± 0.49	9.16 ± 1.57
	Sillicone Gel group, mean ± SD	1.71 ± 0.49	2.14 ± 0.38	2.14 ± 0.38	2.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	9.99 ± 1.25
	%intragroup difference	0.58%	-9.35%	-6.54%	-	-17%	-33%	-8.30%
	Statistical significance (p,α= 0.05	NS (p=0.97)	NS (p=0.19)	NS (p=0.31)	NS	NS (p=0.07)	S (p<0.01)	-
After 3 month								
Intragroup	**REGEN-SIL® group**, mean ± SD	0.61 ± 0.50	0.72 ± 0.46	0.72 ± 0.46	0.72 ± 0.46	0.50 ± 0.51	0.72 ± 0.46	3.99 ± 2.85
	Sillicone Gel group, mean ± SD	0.86 ± 0.38	1.14 ± 0.38	0.86 ± 0.38	1.29 ± 0.49	0.71 ± 0.49	0.57 ± 0.53	5.43 ± 2.65
	%intragroup difference	-29.07%	-36.84%	-16.28%	-44.19%	-29.58 %	-20.83%	-26.31 &
	Statistical significance (p,α= 0.05	NS (p=0.18)	S (p=0.02)	NS (p=0.53)	S (p=0.01)	NS (p=0.33)	NS (p=0.51)	-

N – number of patients, NS – not statistically significant, S – statitically significat, SD – standard deviation

With the exception of the vascularity and pliability score, as shown in **Table 11** and **Figure 13, 14 and 15**, insignificant differences were recorded between groups, in

patients older than 60 years, at 3 months after treatment onset.

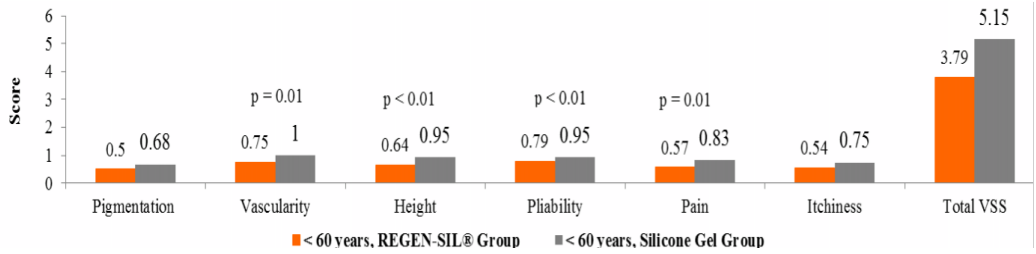


Figure 12. VSS score difference between REGEN-SIL® and Silicone Gel group – patients < 60 years at 3 months after treatment onset (statistically significant at $p < 0.05$ within intergroup)

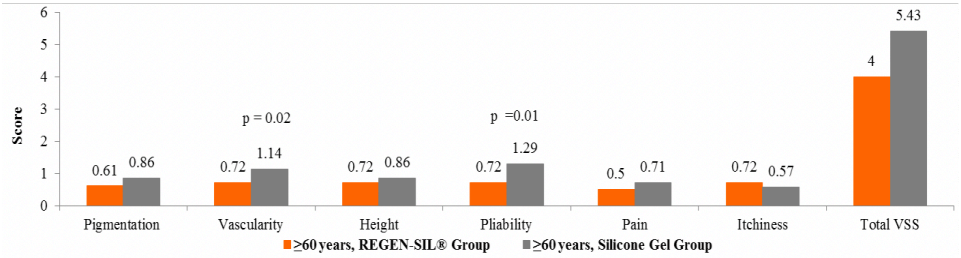


Figure 13. VSS score difference between REGEN-SIL® and Silicone Gel group – patients ≥ 60 years at 3 months after treatment onset (statistically significant at $p < 0.05$ within intergroup)

Administration of REGEN-SIL® proved a significant decrease in VSS compared with Silicone Gel group: vascularity (-36.84%, $p = 0.02$), pliability (-44.19%, $p = 0.01$) (Table 12). The difference in terms of total VSS score was maintained after 3 months in favour of REGEN-SIL® treatment (-26.31% compared to total VSS in Silicone Gel group, after 3 months) in patients older than 60 years.

Safety assessment

No side effects were recorded and compliance was optimal in both groups.

1.3.3.5. *Patient and physician satisfaction*

There was no significant difference between groups regarding satisfaction of patients after 1 month, but significant differences were recorded after 3 months. The cosmetic results of treatment were appreciated as very good and excellent by 95.65% of patients treated with REGEN-SIL® versus 82.98% treated with Silicone Gel, after 3 months. A remarkable difference was recorded after 3 months for overall satisfaction: 97.83% of patients assessed the overall satisfaction of REGEN-SIL® treatment as being very good andexcellent compared to only 82.98% of patientstreated with Silicone Gel (**Table 12**, **Figure 16**).

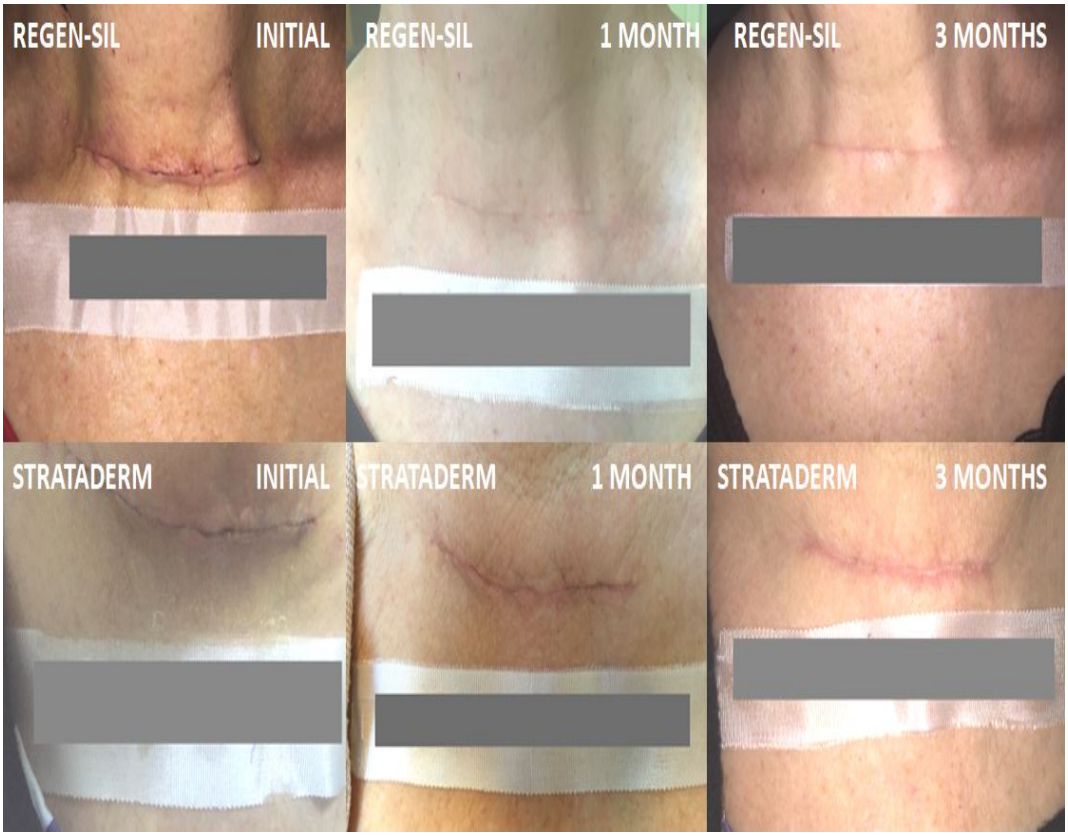


Figure 14. After 60 years old scars assessment

Figure 15. Before 60 years old scars assessment

Table 12. Patient satisfaction

Patient satisfaction	After 1 month (1st follow-up)					After 3 months (2nd follow-up)				
	Mean ± SD	Intergroup Statistical Significance (p,α= 0.05)	%patients			Mean ± SD	Intergroup Statistical Significance (p,α= 0.05	%patients		
			Good	Very good	Excellent			Good	Very good	Excellent
Cosmetic results										
REGEN-SIL® group (n=46)	4.48 ± 0.51	NS, p = 0.260	-	52.17	47.83	4.48 ± 0.51	S, p = 0.045	4.35	13.04	82.61
Sillicone Gel group (n=47)	4.36 ± 0.61		6.38	51.06	42.55	4.51 ± 0.78		17.02	14.89	68.09
Overall satisfaction										
REGEN-SIL® group (n=46)	4.50 ± 0.51	NS, p = 0.040	0.00	50.00	50.00	4.87 ± 0.40	S, p = 0.001	2.17	8.70	89.13
Sillicone Gel group (n=47)	4.26 ± 0.64		10.64	53.19	36.17	4.47 ± 0.78		17.02	19.15	63.83

N – number of patients, NS – not statistically significant, S – statitically significat, SD – standard deviation

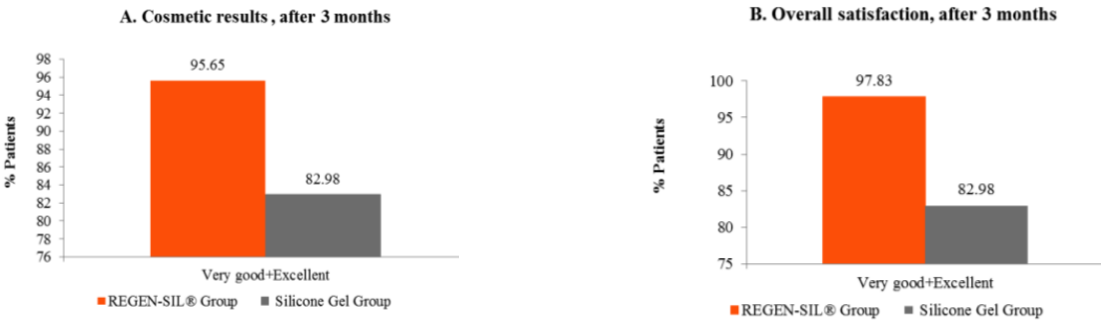


Figure 16. Patient satisfaction

An important difference regarding physicians satisfaction was recorded after 3 months of treatment: physicians have appreciated the overall satisfaction as being very good and excellent for 95.66% patients treated with REGEN-SIL® compared to only 74.47% patients treated with Silicone Gel (**Table 13, Figure 17**).

Figure 17. Physician satisfaction

Table 13. Physician satisfaction

Physician satisfaction	After 1 month (1st follow-up)					After 3 months (2nd follow-up)				
	Mean ± SD	Intergroup Statistical Significance (p,α= 0.05)	%patients			Mean ± SD	Intergroup Statistical Significance (p,α= 0.05	%patients		
			Good	Very good	Excellent			Good	Very good	Excellent
Cosmetic results										
REGEN-SIL® group (n=46)	4.63 ± 0.61	NS, p = 0.145	6.52	23.91	69.57	4.76 ± 0.48	NS (0.882)	2.17	19.57	78.26
Sillicone Gel group (n=47)	4.63 ± 0.74		14.89	27.66	57.45	4.75 ± 0.57		6.38	80.85	12.77
Overall satisfaction										
REGEN-SIL® group (n=46)	4.76 ± 0.43	S, p = 0.003	-	23.91	76.09	4.72 ± 0.54	S (p < 0.001)	4.35	19.57	76.09
Sillicone Gel group (n=47)	4.38 ± 0.77		25.53	29.79	44.68	4.19 ± 0.82		25.53	29.79	44.68

N – number of patients, NS – not statistically significant, S – statitically significat, SD – standard deviation

This study aimed to assess both efficacy and safety of REGEN-SIL® in therapeutic management of post-operative scars and to compare the efficacy and safety of REGEN-SIL® versus another silicone gel available on Romanian market. Both products are authorized as medical devices with the same therapeutic indication. The baseline evaluation of surgical scars revealed no statistically significant differences in VSS score. All parameters of VSS, with exception of itchiness score were recorded as being significantly lower in REGEN-SIL® group compared with Silicone Gel group, after 3 months of treatment. Total VSS score decreased by 63.23% in REGEN-SIL® group, compared with baseline. The total VSS score decreased more in REGEN-SIL® than in Silicone Gel group, the difference between groups being 26% after 3 months of treatment.

1.3.4. Discussions

The recorded results are similar to those presented by other clinical trials. Medhi et al., (Medhi et al., 2013) evaluated the efficacy of silicone gel (Kelo-cote®, Wockhardt Limited, Mumbai, India) for prevention of post- operative hypertrophic and keloid scars. The recorded decreases for VSS in present study were in similar trend to those presented by Medhi B et al., (Medhi et al., 2013).

Undoubtedly, silicone-based products are effective in scar management. The efficacy and safety of their administration are supported by numerous studies (Ahn et al., 1991; Conea et al., 2016; Signorini and Clementoni, 2007), and they become the gold standard for scar management (Mustoe, 2008). Numerous silicone-based products are available on pharmaceutical market, but clinicians should select products, considering their sustained efficacy and safety.

Kim et al., (Kim et al., 2014) compared the efficacy of silicone gel (Kelo-CoteTM, SejongMedix, Seoul, Korea) versus silicone sheets (ScarclinicTM-Thin, Hans Biomed, Seoul, Korea) in preventing of the post- surgical scars and no significant differences were recorded between silicone gel and silicone sheets. Scar evolution was similar to that recorded in the current study (Kim et al., 2014).

The younger patients were most targeted in our comparative evaluation, because it is commonly recognized that a temporal delay in wound healing, but not in quality of healing, occurs in elderly comparing to young patients (Guo and Dipietro, 2010).

The slow metabolism rate and less tensile strength determine the low chance to develop hypertrophic and keloid scars in elderly (Li-Tsang et al., 2005). Younger patients displayed a prolonged high turnover state and a retarded rate of maturation compared with patients older than 55 years that displayed an accelerated maturation (Bond et al., 2008).

This observation is attributed to skin physiology related on age: the young skin has more elastic fibres which lead to a greater tension and the rate of collagen synthesis is greater in young people (Rabello et al., 2014).

More delayed wound healing with a better quality of scarring process in patients older than 60 years was remarked in our investigated group, also. An increasing trend of VSS scores were recorded for patients younger than 60 years compared to patients older than 60 years, after 1 month of treatment onset, but without statistical significance in both groups. Treatment with both silicone-based products equilibrated the difference between age groups, and a decreasing of VSS scores was remarked for patients younger than 60 years compared to those recorded for patients older than 60 years, at 3 months after treatment onset.

The comparative assessment of scarring process depending on age revealed that REGEN-SIL® is more efficient than the comparative product in post- operative scar management both in young and elderly patients. Total VSS score decreased more in REGEN-SIL® group than in Silicone Gel group. The differences between groups were 26.49% at patients younger than 60 years and 26.31% at patients older than 60 years, respectively in favour of REGEN-SIL®, at 3 months after treatment onset. No side effects were recorded in both groups, which support optimal tolerability of silicone-based products.

A wound protector made of silicone has already been demonstrated to significantly prevent the drying of the surgical wound and to reduce the incidence of infection [9], and it

has been widely used during endoscopic (laparoscopic, thoracoscopic) surgery. However, there is no available product that can be used during thyroid surgery (Lee et al., 2017).

Many surgical methods have been attempted for increasing cosmetic satisfaction. Some surgeons have attempted using robots or endoscopes to place the incision site in an invisible position in the axillary or periareolar area rather than the neck (Katz et al., 2012).

Others have attempted to reduce the incision length, but this does not necessarily lead to improved patient satisfaction with the aesthetic outcomes (Toll et al., 2012).

One study compared the aesthetic appearance of cervical incisions closed with tissue glue (octyl-cyanoacrylate) versus subcuticular absorbable sutures and found that the subcuticular sutures provided better aesthetic outcomes with small cervical incisions in the early phase after thyroid surgery (Consorti et al., 2013).

The wound healing process consists of the inflammatory (immediate to 2 to 5 days), proliferative (2 days to 3 weeks), and remodeling (3 weeks to 2 years) phases, and therefore, 2 years after an operation, the end of the remodeling phase, is considered appropriate for evaluating the final states of wounds (Jablonka et al., 2012).

This study has the limitation to assess the efficacy and safety only after 3 months of treatment and no other follow-up was stipulated in clinical trial protocol after 3 months. No other observations were carried out for scar progression. Another limitation is assessment of scarring process between the two sexes, because the assessed lot included only female, taking into account the high prevalence of thyroid and parathyroid pathology in female.

As in many previous clinical studies reported, the efficacy of silicone-based products is demonstrated on all types of scars: burn scars (Momeni et al., 2009), post laser exfoliation erythema, hypertrophic and keloid scars (Chernoff et al., 2007).

Further studies are necessary in order to investigate if REGEN-SIL® provides more efficacy than other topical silicone-based products on scarring of wounds situated in different anatomical sites. Skin of shoulders, neck, presternum, knees and ankles are more susceptible to high tension thus developing hypertrophic scars whereas keloid scars are developed with predilection on anterior chest, earlobes, upper arms and cheeks.

At present, various scar assessment scales are available, but not one has been shown to be reliable, consistent, feasible, and valid at the same time. The existing scar assessment scales appear to attach little weight to the opinion of the patient. The newly developed Patient and Observer Scar Assessment Scale consists of two numeric scales. Both scales have to be completed by the patient and the observer, respectively (Draaijers et al., 2004).

The patient scale's consistency and the observer scale's consistency, reliability, and feasibility have been tested in many studies (Nedelec et al., 2000).

For the Vancouver Scar Scale, which is the most frequently used scar assessment scale at present, the same statistical measurements could be examined and compared with the others (Moiemen et al., 2001).

Linear regression of the general opinions on scars of the observer and the patient showed that the observer's opinion is influenced by vascularization, thickness, pigmentation, and relief, whereas the patient's opinion is mainly influenced by itching and the thickness of the scar. Such an impact of itching and thickness of the scar on the patient's opinion is an important and novel finding. The Patient and Observer Scar Assessment Scale offers a suitable, reliable, and complete scar evaluation tool (Beausang et al., 1998).

The actual research was focused to assess the comparative efficacy and safety of REGEN-SIL® versus another silicone gel available on pharmaceutical market, in therapeutic management of post-operative scars. This research is justified by structural variety of silicones, but also by the quantitative ratios between silicones that individualizes silicone-based topical products. It is, under our knowledge, the first study that compared the efficacy and safety of two silicone-based gels, the results of actual study being in interest oftherapeutic decision for health care professionals.

Laser therapies are used prophylactically for excessive scar formation. The Laser-Assisted Skin Healing treatment induces a controlled heat stress that promotes tissue regeneration. This comparative trial is the first to evaluate the performance of a new automated 1210-nm laser system, compatible with all Fitzpatrick scale phototypes. This new 1210-nm laser treatment, used as a single session performed immediately after surgery, provides significant objective and subjective improvements in scar appearance. These data can be useful when preparing patients to undergo their surgical procedure (Casanova et al., 2017).

The current study determined that REGEN- SIL® is more efficient than the comparative product in therapeutic management of post-operative scar. The difference between the two products in terms of efficacy is explained by the complex formula of REGEN-SIL® that contains 4 types of silicones: high and low molecular dimethicone, trimethyl- siloxisilicate and dimethicone crosspolymer. High and low molecular dimethicone form a protective, fine and hydrophobic barrier on the skin and leaves a silky and un-sticky sensation, trimethylsiloxisilicate creates rapidly a persistent and protective hydro- phobic film and dimethicone crosspolymer creates a gel structure.

1.3.5. Conclusions

In conclusion, there are numerous available silicone- based products used for management of scars, but the first choice of the clinicians should be based on both efficacy and safety of the product. The results of this study indicate that REGEN-SIL®, a complex silicone gel is both efficient and safe in therapeutic management of post-operative hypertrophic and keloid scars, being more efficient than the comparative product and more appreciated by patients and physicians.

1.4. BIOCHEMICAL MARKERS IN ENDOCRINE SURGERY

1.4.1. Introduction

Calcium metabolism refers to the circulations and regulation of calcium ions (Ca2+) in and out of various body compartments, such as the gastrointestinal tract, the blood plasma, the extracellular and intracellular fluids and bone tissue. An important aspect of

calcium metabolism is plasma calcium homeostasis, the regulation of calcium ions in the blood plasma within narrow limits (Brini, 2013).

In this process, bone tissue acts as a calcium storage center for deposits and withdrawals as needed by the blood, via continuous bone remodeling. Derangement of this mechanism leads to hypercalcemia or hypocalcemia, both of which can have consequences for health. The level of the calcium in plasma is regulated by calcitonin and parathyroid hormone (PTH); calcitonin is released by the thyroid gland when its plasma level is above its set normal point (in order to lower calcium level); PTH is released by the parathyroid glands when calcium level falls below set point (in order to raise it) (Marieb, 2000).

Inorganic phosphorus in the form of the phosphate $PO3{-}4$ is required for all known forms of life (Ruttenberg, 2001).

Phosphorus plays a major role in the structure of DNA and RNA. Living cells use phosphate to transport cellular energy with adenosine triphosphate (ATP), necessary for every cellular process that uses energy. ATP is also important for phosphorylation, a key regulatory event in cells. Phospholipids are the main structural components of all cellular membranes. Calcium phosphate salts assist in stiffening bones. Biochemists commonly use the abbreviation "Pi" to refer to inorganic phosphate (Lipmann, 1944).

Every living cell is encased in a membrane that separates it from its surroundings. Cellular membranes are composed of a phospholipid matrix and proteins, typically in the form of a bilayer. Phospholipids are derived from glycerol with two of the glycerol hydroxyl (OH) protons replaced by fatty acids as an ester, and the third hydroxyl proton has been replaced with phosphate bonded to another alcohol (Nelson, 2000).

The thyroid function damage by a tumour modifies both directly and indirectly the phosphocalcic metabolism. Direct damage is the consequence of malignant transformation of thyroid functional tissue. Indirect damage is caused by the surgical removal of the thyroid and/or parathyroid glands as well as oncological treatment. In patients with advanced or metastatic thyroid cancer, the vandetanib tyrosine kinase inhibitor has endocrine effects. The consequences of biological changes on phosphocalcic metabolism and gonadotrope and adrenal function are unknown (Ellai, 2011).

Postoperative hypoparathyroidism is most commonly caused by the extirpation, injury or devascularisation of parathyroid glands. It can be considered a medical and surgical emergency (Kazaure and Sosa, 2018).

Thyroid cancer is a rare entity among human malign tumours, covering less than 1% of all cancers, but is the most common endocrine malignancy. The incidence of thyroid cancer in the US is about 7.7 per 100,000 inhabitants/year. Of the histological types, the highest incidence is papillary, 5.7 per 100,000 inhabitants/year, followed by follicular and then medullary form. The incidence of thyroid cancer has increased by about 5% annually over the past 10 years and the mortality rate has increased from 0.8% per year from 2002 to 2011 (Cooper et al., 2009; Nguycn et al., 2015).

Women are 3-4 times more often affected than men. The effect of Graves disease on the postoperative complications in patients undergoing total thyroidectomy is unclear. This difference may reflect not only real incidence, but also difficult access to medical services and early detection (Kwon et al., 2019).

The staging of thyroid cancer is based on TNM (Tumor, Nodes, Metastases), with a few peculiarities of other cancers. Thus, both the histological diagnosis and the age of the patient are taken into account in the evaluation of the prognosis and the establishment of the therapeutic course. Clinical staging is performed by inspecting and palpating the thyroid gland and regional lymph nodes. Laryngoscopy is also indispensable for highlighting the mobility of vocal cords. Paraclinical examinations include radioactive isotope, ultrasonography, computer tomography and MRI scanning. Diagnosis of thyroid cancer should be confirmed by puncture-needle biopsy or open biopsy. Staging should be completed by a biopsy on suspected lymph node (Edge and Compton, 2010).

Recent studies has been increasing pressure for early discharge of patients undergoing total thyroidectomy. While some surgeons place all patients on calcium postoperatively, others use this medication more selectively with biochemical and/or clinical factors guiding their decision. Postoperative PTH and calcium levels, as well as clinical factors, such as lymph node dissection, autotransplantation, and indication for thyroidectomy have been studied to anticipate the need for calcium supplementation and predict the development of hypocalcemic symptoms (Cayo, 2012; Carter, 2014; White et al., 2016).

While biochemical studies of post thyroidectomy patients have demonstrated PTH levels at various times correlate with the development of symptomatic hypocalcemia, the optimal timing remains unclear. Postoperative serum calcium on the day one has not been shown to consistently correlate with symptomatic hypocalcemia (Lombardi et al., 2004; Sywak et al., 2007; Wang et al., 2011; Edafe et al., 2014; Islam et al., 2014; Le et al., 2014).

Parathyroid hormone hypersecretion characterizes abnormal activity of one or more parathyroid glands. Primary hyperparathyroidism is a common hormonal disorder, third in the order of importance after diabetes and hyperthyroidism (Gopinath and Mihai, 2011; Cordellat, 2012).

In this study we analyze hyperparathyroidism in all its aspects, including general information, types of hyperparathyroidism, diagnosis procedures, and the specific treatment.
The parathyroid glands are oval in shape, and their total weight is about 30 mg in men and 35 mg in women (Johnson, 2005), the color varies in relation with age and blood flow. Appearance is lighter in color than the thyroid gland, varying between yellowish-reddish and reddish-brown in surgery. In women, during pregnancy, they are more voluminous and more intense colored.

Structurally, the parathyroid glands are made up of two types of cells: chief cells, which synthesize and release parathyroid hormone (PTH), and oxyphil cells which increase in number with age and have an unknown function. Parathormone controls the metabolism of calcium and phosphorus and helps in maintaining a constant relationship in blood. An adequate amount of calcium is essential for the normal functioning of the heart, the nervous system, the osteomuscular system and the kidneys (De Lellis, 1993).

PTH increases the body's ability to absorb calcium from food and its reabsorption to the kidneys. Calcium is deposited in bones that provide them resistance, but constant amounts of calcium are deposited and removed, depending on the body's needs. This process would not be possible without PTH intervention (Selby, 2011; Silverberg et al., 1999).

Calcium is the only mineral in the body that has a mechanism of regulation through the parathyroid glands. No other gland has this role on another mineral. When the amount of calcium rises above the normal limits, respectively, falls below the normal range, there were obeserved body disturbances and changes in the patients personality. Dysfunction of parathyroid glands is not only about osteoporosis or kidneys calculi, it is a problem related to how the patient feels mentally and that he is unable to enjoy life (Pallan and Khan, 2011; Roth, 1970).

There is a significant statistical correlation between the percentage change in the PTH decrease and the development of postoperative hypocalcemia, but a cut-off definition is more difficult than in primary hyperparathyroidism. With a cutoff value of 50% (a 50% decrease in PTH1 level compared with PTH2 level), the risk of postoperative hypocalcemia is less than 70%. To have a high predictive value it is necessary to increase the cut-off value to 69%. In this way it is possible to predict patients with a postoperative hypocalcemia risk of 93.3%, although a certain hypoparathyroidism can be observed with a 76% change in PTH decrease in value (positive predictive value, 100%) (Scurry et al., 2005; McLeod et al., 2006).

Recent studies reported that the serum calcium level on the first postoperative day correlates with the absolute postoperative PTH level to predict patients at risk of hypocalcemia. Moreover, considering the absolute postoperative PTH level, to have a clinically useful predictive value it is necessary that the PTH levels decrease under normal values (Toniato et al., 2008; Lombardi, 2006; Nahas, 2006).

Postoperative hypoparathyroidism is one of the most common complications following total thyroidectomy and its primary cause is secondary hypoparathyroidism after direct injury, devascularization, obstruction of venous drainage, or inadvertent excision of the parathyroid gland (PTG) (Shaha, 1998; Bliss, 2000). Serum calcium and phosphorus levels are reliable predictors of clinically relevant hypocalcemia after total thyroidectomy (Cho, 2016).

The main objective of this study is to establish correlations between the advanced thyroid cancer staging, the choice of individual treatment, the results obtained, the frequency and intensity of transient and/or permanent postoperative hypocalcemia. The results of the study are compared with the data from the literature as well as with the previous experience of the 3rd Surgery Unit of St. Spiridon Iasi Hospital, in order to highlight the causes of these complications. This creates opportunities for developing surgical, oncological and endocrine managements protocols for patients diagnosed with advanced thyroid cancer in order to avoid these relatively frequent and important complications.

We have also aimed to assess the effects of parathyroid hormone hypersecretion in a group of patients diagnosed with primary hyperparathyroidism.

1.4.2. Materials and methods

The material of this study consists of two groups of patient (I and II), evaluated during the same period of time for postoperative complications: hypocalcemia and hypoparathyroidism. The two studies are related each over by the most common complication of thyroidectomy which could occur - hypocalcemia.

Most of the patients were investigated and diagnosed under a prior admission to the Endocrinology Clinic. The evaluation consisted in general and clinical examinations, serum levels of thyroid hormones, parathormone and calcium. The otorhinolaryngological clinical examination and thyroid ultrasonography were also performed.

Indirect laryngoscopy was performed in order to identify possible paralysis of vocal cords, eventual compression or invasion of thyroid nodules. In most cases, thin needle biopsy puncture and computer tomography were performed. This highlights the anatomical extension of the tumour and the possible invasion of adjacent structures, thus guiding the extent of surgery.

1.4.2.1. Group I - Hypocalcemia after oncologic thyroidectomy

We conducted a retrospective study on 213 cases of thyroid cancer, operated in the 4th Surgery Clinic of the "St. Spiridon" Emergency Clinical Hospital in Iasi between January 2012 and December 2018. In particular, 116 cases diagnosed in advanced stages (III and IV) were analyzed in the Endocrinology Clinic of the St. Spiridon Clinical Hospital.

From the studied group 194 patient underwent surgical inteventions for thyroid cancer. Of these, 145 were performed in female and 49 in male patients, achieving an M: W ratio of 1: 2.95.

The data were taken from the table provided by the statistical service of the St. Spiridon Clinical Hospital, as well as from the surgery protocols and histopathological exams. The inclusion criteria in the batch were the primary or secondary diagnosis of malignant thyroid cancer and the over 18 years of age in both genders.

1.4.2.2. Group II - Phosphocalcic equability after oncologic parathyroidectomy

In this study, we investigated 200 patients with hyperparathyroidism, admitted in "St. Spiridon" Emergency Clinical Hospital in Iasi, observing their anamnesis, symptoms, checking the investigations performed and the prescribed treatment for each patient.

The evolution of the disease has been noted by age groups, years, and genders, as well as associated comorbidities.

In the study we evaluated the diagnosis statistic of patients admitted in hospital during 01.01.2008-10.07.2018. The statistical analysis was done using Microsoft Excel.

We performed hystological examination of the tumours on both groups and compared the results with the postoperative evolution. Tissue samples were fixed in formalin, embedded in paraffin blocks (10%), sectioned at 4-μm thickness, and stained routinely with Hematoxylin–Eosin (HE) and Verhoeff-van Gieson for collagenic and elastic fibers.

An immunohistochemical assessment was performed for cellular phenotyping using monoclonal antibodies against Synaptophysin (clone 27G12, Novocastra, dilution 1:300), Chromogranin (clone 5H7, Novocastra, dilution1:400), TTF1 (Thyroid Transcription Factor 1) (clone SPT24, Novocastra, dilution 1:200), Thyroglobulin (clone 1D4, Novocastra, dilution 1:70), Ki 67 (clone SP6, Thermo Scientific, dilution 1:200), CD31 (Endothelial Cell Marker) (clone NCL-CD31-1A10, Novocastra, dilution 1:100) and Calcitonin (clone CL 1948, Novocastra, dilution 1:200).

1.4.3. Results

1.4.3.1. Results of the group I – patients with hypocalcemia after oncologic thyroidectomy

Percentage of female patients accounted for 74.74% of all cases, while male patients accounted for 25.25% (**Figure 18**) .

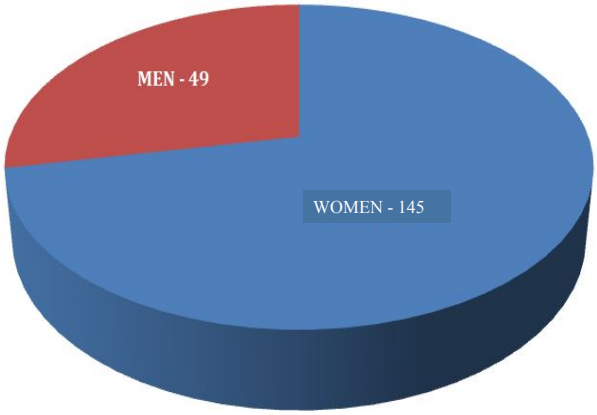


Figure 18. Distribution by gender within the study group

Distribution by age group shows the proportion of the disorder in patients over 50 years of age (**Figure 19**).

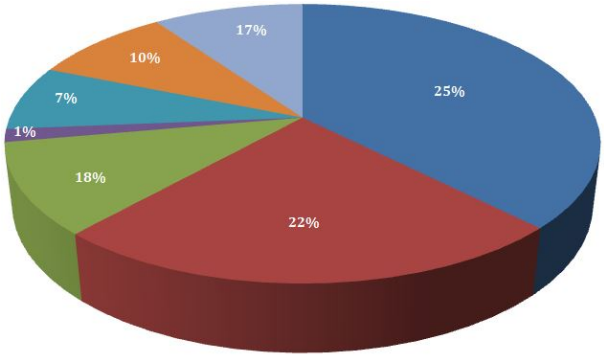


Figure 19. Percentual distribution of patients by age: 1% between 18-20, 7% between 21-30, 10% between 31-40, 17% between 41-50, 18% 71 and on, 22% between 51-60 and 25% between 61-70 years old

Thus, out of a total of 194 cases, patients aged 61-70 years are the highest age group, with 49 cases and 25.52%, followed by the 51-60 age group, accounting for 22% of the total cases - 43 patients.

The fourth decade of life includes 33 patients, 31-40 year-old patients are 18 cases, while 18-30 year-old patients are 16 cases.

Patients over the age of 71 mark a decrease in incidence after the peak of 61-70 years, including 35 cases - 18.2% of the total. The minimum age in the study group is 19 years old and the maximum of 84 years old and a medium age of 55.3 years (**Figure 20**).

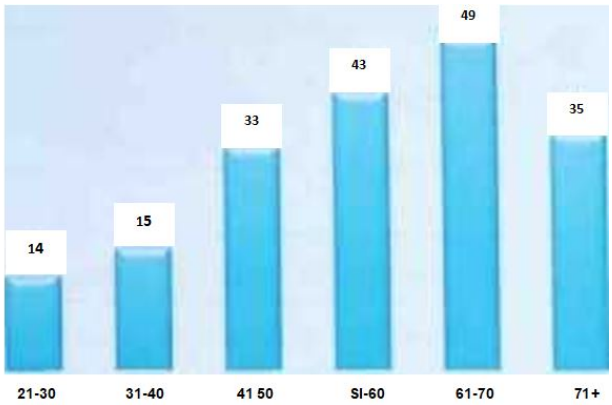


Figure 20. Patients distribution by age

To analyze the distribution of thyroid cancers subtypes among the investigated patients, we took the data from the results of their histopathological exams. Of the 194 cases considered, the highest histological weight is papillary thyroid cancer (**Figure 21**), with 79.89% of the total cases. This is followed by medullary thyroid cancer with 27 cases, anaplastic thyroid cancer - 17 cases and follicular thyroid cancer - 7 cases.

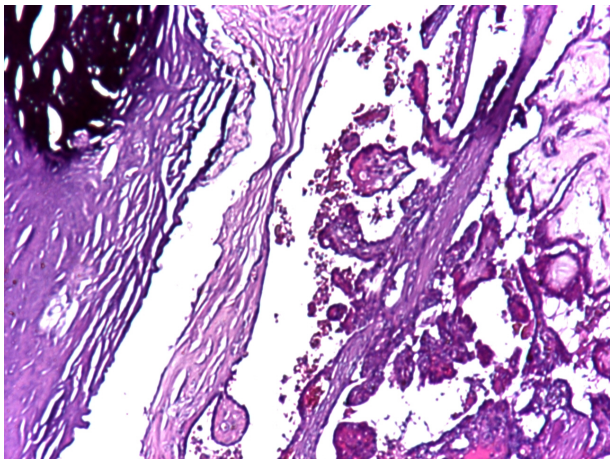
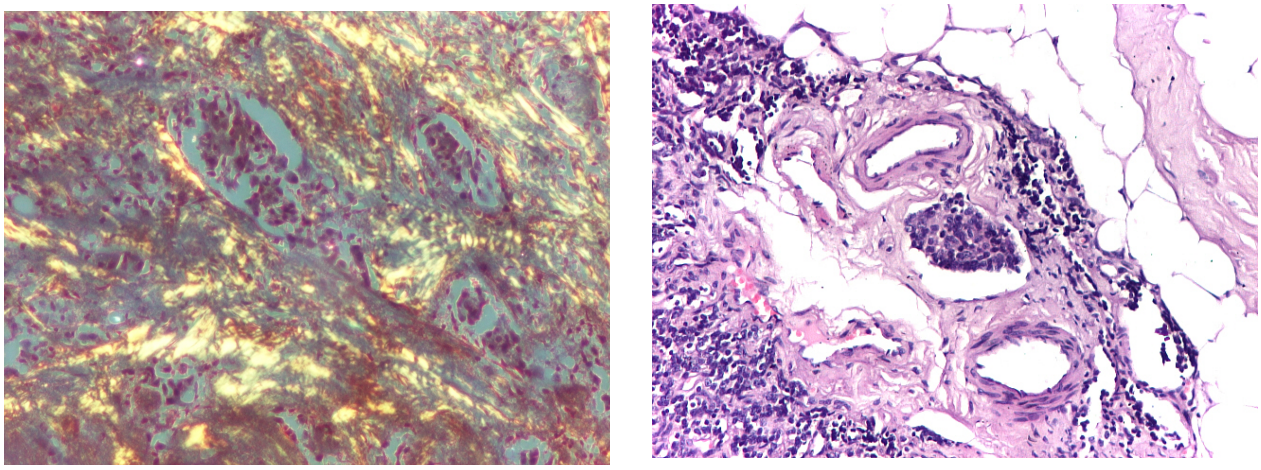


Figure 21. Conventional papillary carcinoma, HE, x 10

Three other cases were non-thyroidal cancers: a case of neuroendocrine tumour, a thyroid locomotor plasmocytoma and a renal neoplasm metastasis case.

Medullary thyroid cancer (**Figure 22, a, b**) is distributed relatively constant between the four age groups: 3 cases (11.5%) for the age group 45-50 years, 2 cases (7.69%) corresponding to the 5th decade of life, 5 cases (13.51%) for 61-70 years and 2 cases (7.4%) for patients over 70 years of age (**Figure 23**).



a. Dicroism amyloid deposits, polarized light, x 4. **b.** Intravascular tumour embolism, HE, x 10

Figure 22. Medullary thyroid carcinoma

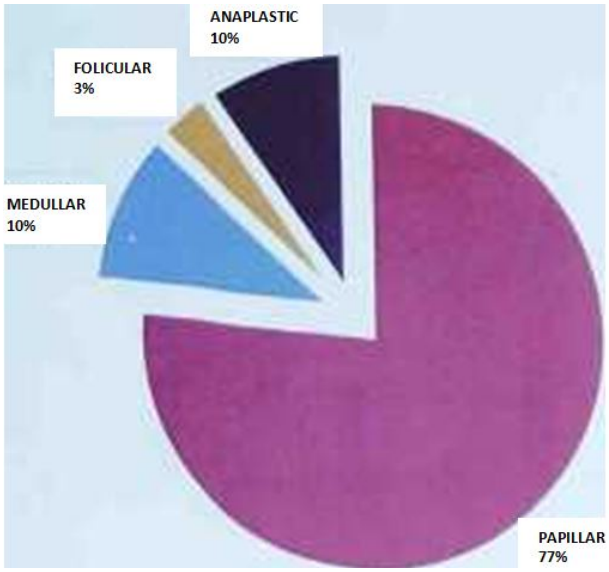
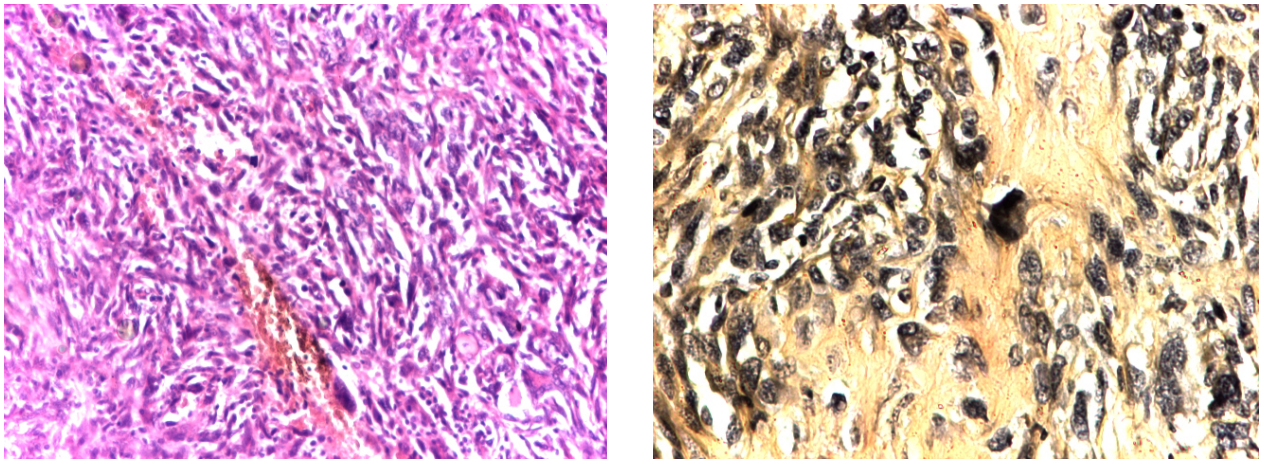


Figure 23. Thyroid cancer type percentage

Analyzing the relationship between the histological subtype and the age for advanced cancers, it can be observed how the proportion of papillary thyroid cancer decreases from 88.46% for the age group of 45-50 years, to 84.61% for the age group 51-60 years at 54.05% for 61-70 years and only 66.66% for patients over 70 years of age.

Anaplastic thyroid (**Figure 24**) cancer increases from 0 cases for the 45-50 age group, 2 cases (7.69%) for 51-60 years, 7 cases for 61-70 years (18.9%) and 7 cases (25.92%) for patients aged over 70 years. Follicular thyroid cancer occurs only in the age group of 61-70 years, in a number of 5 cases.



a. fused cell and hemorrhage areas, HE, x 10. **b.** pronounced pleomorphism, VG, x 20

Figure 24. Anaplastic thyroid cancer.

The rate of intraoperative complications related to recurrent laryngeal nerve injury, intraoperative haemorrhage requiring haemostasis and the necessity to achieve a definitive tracheostomy is 13%, 17% and 3.44%, respectively (**Table 14**).

Regarding the rate of postoperative complications, these are present in 26.72% of patients, while the complications strictly related to the operative act are 17.24%. By excluding short-term complications (transient hypocalcaemia and postoperative haemorrhage), it appears that a number of 16 complications were the direct consequence of the operative act. A total of 12 patients (10.34%) experienced these complications (**Table 14**).

Transient hypocalcaemia (16 cases, 29% of all complications), defined as 6-month remission hypocalcaemia, was associated with complications related to the operative act whereas permanent hypocalcaemia required supplemental calcium medication throughout life (4 cases, 7.27% of total complications). This is the consequence of parathyroid gland damage during total thyroidectomy intervention (**Table 14**).

1.4.3.2. Results of the group II – patients with phosphocalcic equability after oncologic parathyroidectomy

In group II it can be observed that a much higher percentage of women than men are suffering from this pathology. This involves a dificult diagnosis of patients with primary hyperparathyroidism because they do not have major clinical symptoms of disease, but only increased blod levels of calcium and PTH (**Figure 25**).

Table 14. Postoperative complications depending on type of the intervention, in the case of advanced thyroid cancers; TT=total thyroidectomy, TL=total lobistectomy, RD=radical dissection of the neck, SD=selective cervical dissection, MRD=modified cervical radical dissection, ETT=extended total thyroidectomy, PTT=permanent tracheostomy, TE=tumor excision, TOT=thyroidectomy totalization

Complications by intervention	TOTAL	TT+ SD	TL+ PTT	ETT+ RD+ PTT	TT	ETT+ MRD	TT+ TE	TE	WS	TT+ MRD	ETT + RD	TT+ RD+ PTT	TT+ PTT	TO T+ RD	TT+ RD	ETT
Oesophageal fistula	1		1													
Fistula of the hypopharynx	1			1												
Tracheal fistula	I				1											
Permanent hypocalcaemia	4	1			2									1		
Unilateral vocal cord paresis	1					1										
Paraseptal emphysema	1									1						
Phrenic nerve paralysis	1									1						
Bilateral vocal cord paresis	1											1				
Unilateral recurrent nerve paralysis	1				1											
Pneumomedias tinum	1												1			
Subcutaneous emphysema	1												1			
Transient hypocalcaemia	16	1		1	3	1	2			2	1	1			2	2
Wound dehiscence	1															
Postoperative bleeding	2			1							1					
Wound infection	1														1	

TT=total thyroidectomy, TL=total lobistectomy, RD=radical dissection of the neck, SD=selective cervical dissection, MRD=modified cervical radical dissection, ETT=extended total thyroidectomy, PTT=permanent tracheostomy, TE=tumor excision, TOT=thyroidectomy totalization

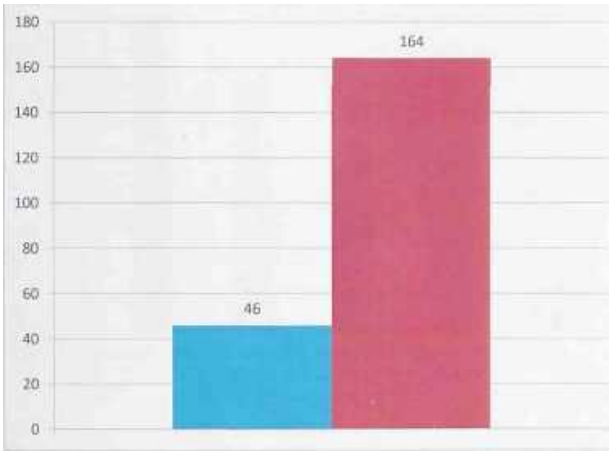


Figure 25. The incidence of primary hyperparathyroidism by genders; blue is the number of men and red number of women.

The investigated patients with primary hyperparathyroidism had the following signs and symptoms: recurrent renal lithiasis, peptic ulcers, psychotic desorders, and less frequently encountered increased bone resorption (**Figure 26**).

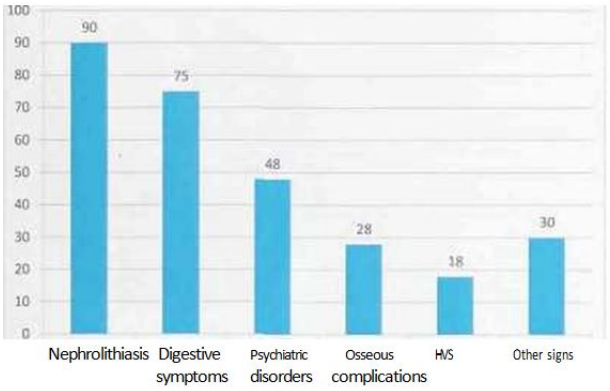


Figure 26. Symptoms associated with hyperparathyroidism

Most of the investigated patients had a single parathyroid gland affected. From the whole group 20% had two or more affected parathyroid glands (**Figure 27**).

This gland with abnormal activity usually has a benign tumour or an adenoma. From an etiopathogenic point of view, MEN I syndrome is most commonly encountered in the causality of this pathology (**Figure 28**).

Most adenomas are located in the lower parathyroid glands (**Figure 29**).

Within the Group II, 40% of the cases have been histologically diagnosed as parathyroid carcinoma and the others as parathyroid adenoma.

In one case of carcinoma, gross examination revealed a 7 cm diameter right parathyroid gland with periglandular fibrosis, thick capsule and multiloculated aspect. On the section was identified a gray-white solid parenchyma without areas of hemorrhage or necrosis.

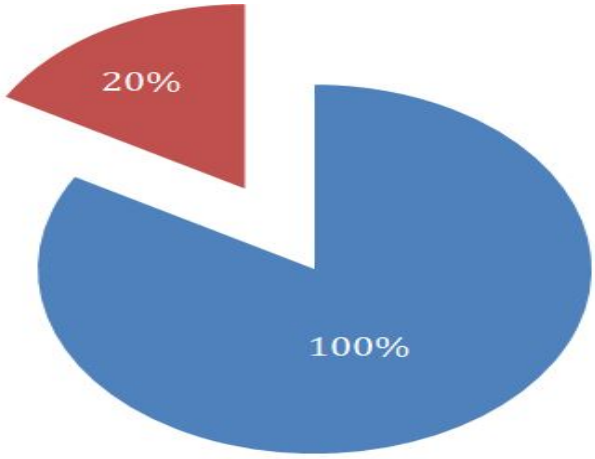


Figure 27. The incidence of hyperparathyroidism according to the number of affected glands.

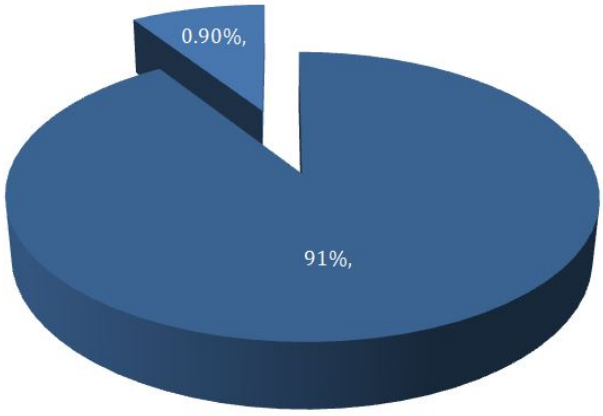


Figure 28. The incidence of MEN I versus other syndromes.

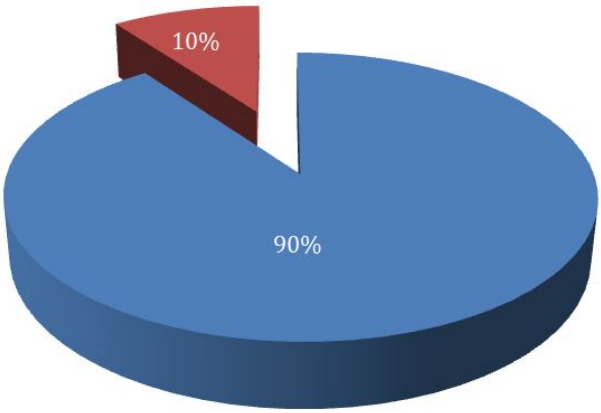


Figure 29. The incidence of adenoma localization: blue represents lower parathyroid adenomas and gray the rest.

On histology parathyroid carcinoma display a solid or trabecular growth pattern with tumour cells closely packed in nests or trabecular pattern with foci of hemorrhage and band-forming fibrosis (**Figure 30**). The tumour was composed of chief cells with pale eosinophilic or clear cytoplasm, round nuclei, isolated pleomorphic hyperchromatic nuclei with occasional pseudoinclusions and rare mitosis. Smooth tumour infiltrates the whole capsule, had periglandular satellite nodules and associated vascular invasion (**Figures 31, 32 and 33**).

The tumour cells were immunopositive for Synaptophysin (**Figure 34**), Chromogranin (**Figure 35**), and negative for Thyroglobulin, calcitonin and TTF1 (**Figures 36, 37 and 38**). Mitotic index was 3% (Figure 10). Vascular invasions were found in capillary spaces or large venous spaces, positive to CD31 (**Figures 39-41**).

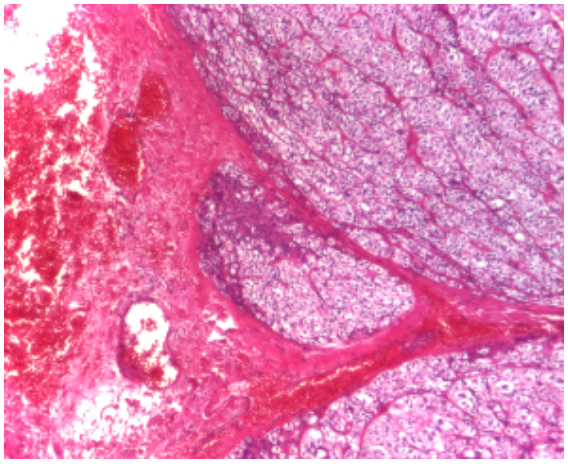


Figure 30. Periglandular satellite nodules with band-forming fibrosis, HE staining, x 40

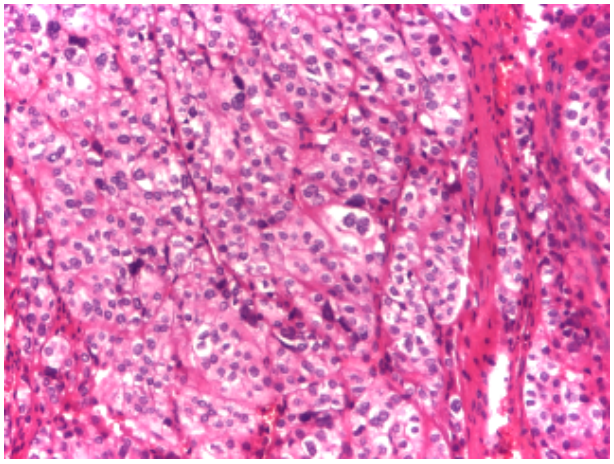


Figure 31. Parathyroid carcinoma composed of chief cells with isolated hyperchromatic nuclei, HE staining, x 1

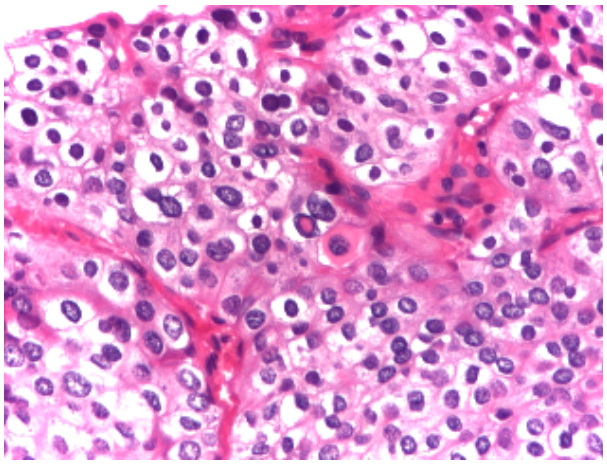


Figure 32. Ocasional nuclei with eosinophilic pseudoinclusion (center), HE staining, x 200

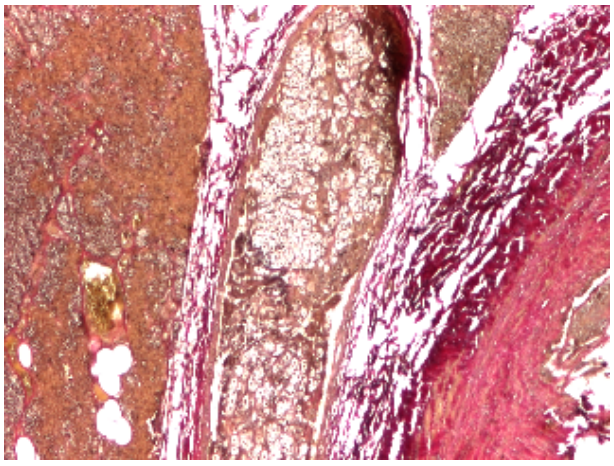


Figure 33. Vascular invasion (center), Verhoeff-van Gieson staining, x 40

At one patient with parathyroid adenoma, gross examination of the right lower parathyroid gland revealed a 2 cm diameter with a round reddish-brown nodule,

homogeneous consistency and a thin capsule. Focal cystic areas are found. A thin rim of normal brown glandular tissue was found on the periphery of the nodule.

Tissue samples were fixed in formalin and embedded in paraffin blocks (10%), sectioned at 4-µm thickness, and stained routinely with Hematoxylin–Eosin (HE), van Gieson and Verhoeff-van Gieson.

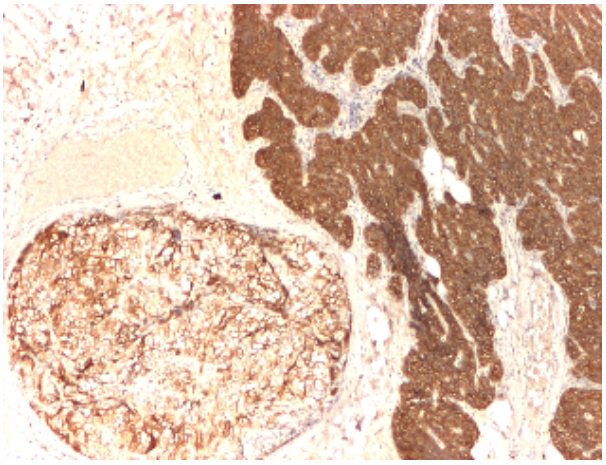


Figure 34. Positive diffuse staining in satellite nodule (left) and normal remaining parathyroid tissue, Synaptophysin, x 40

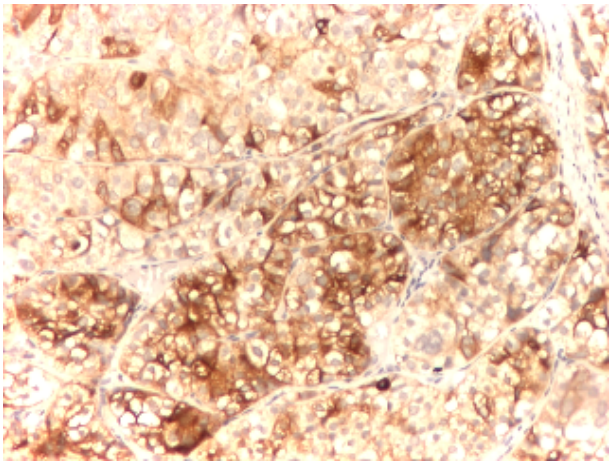


Figure 35. Positive diffuse staining in tumour cells, Chromogranin, x 100

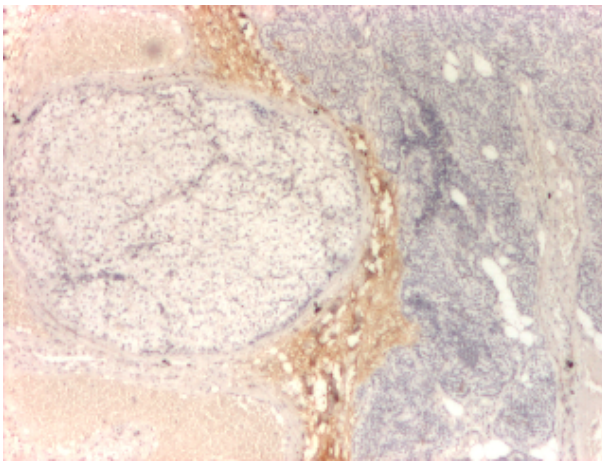


Figure 36. Negative staining for Thyroglobulin in tumour cells (left), x 40

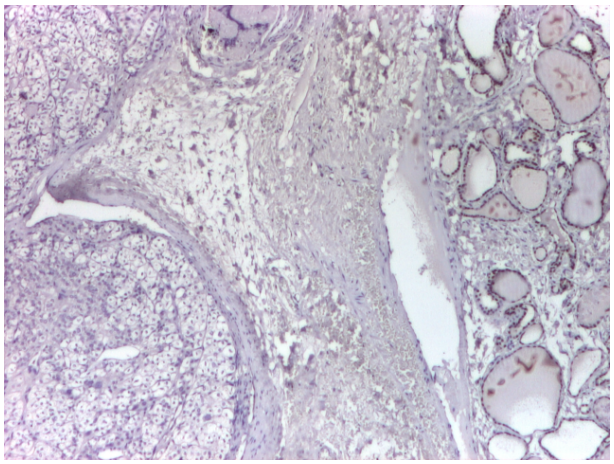


Figure 37. Negative staining for TTF1 in tumour cells (left), x 40

On the histology level a nodular encapsulated neoplasm was found. It had a thin collagenic capsule on the periphery (**Figures 42 and 43**).

The parenchymal cell arrangement was trabecular or solid sheets, with focal acinar pattern and isolated cystic spaces. The lumina of follicular or cystic spaces contained eosinophilic material (**Figures 44 and 45**).

Tumour cells, composed of chief cells, had a pale eosinophilic or vacuolated cytoplasm with round nuclei occasionally with small nucleolus (**Figures 46 and 47**). On the periphery area a small rim of normal parathyroid tissue was found. We have not identified issues of vascular invasion, capsular infiltration, necrosis or hemorrhage.

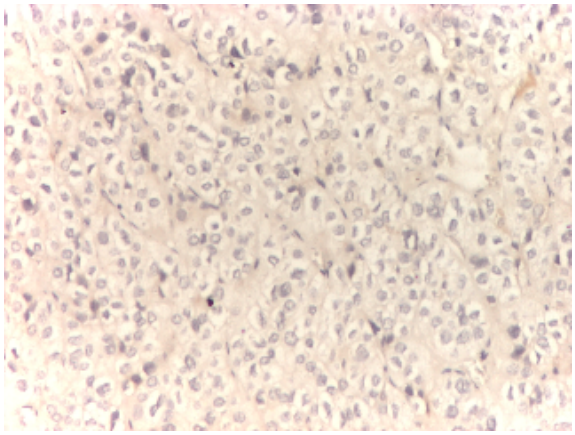


Figure 38. Negative staining for Calcitonin, x 100

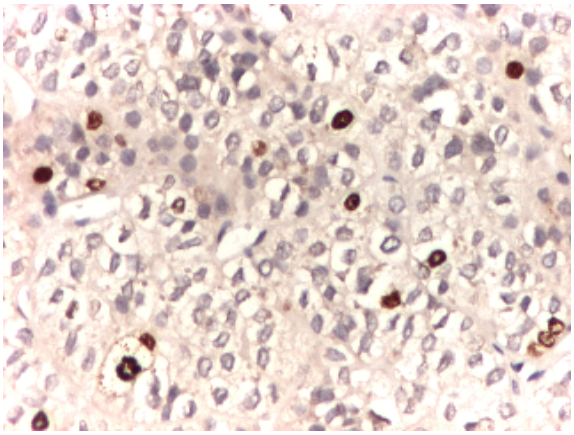


Figure 39. Low mitotic index, ki67, x 200

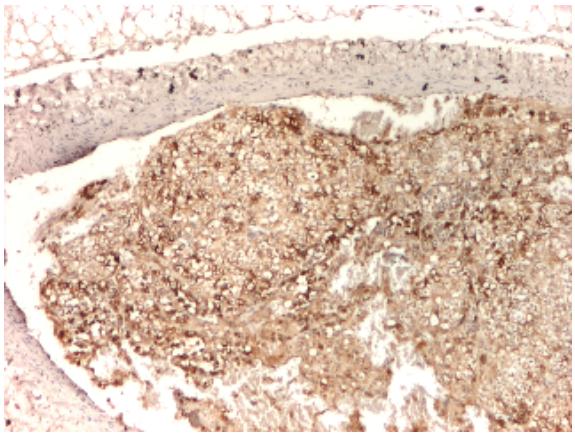


Figure 40. Vascular invasion, positive for Chromogranin, x 40

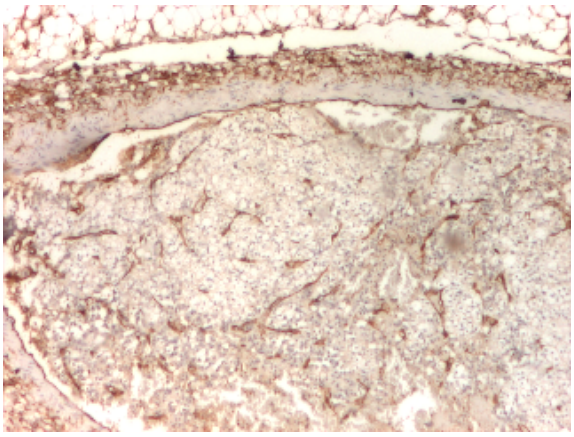


Figure 41. Vascular invasion, positive for CD31, x 40

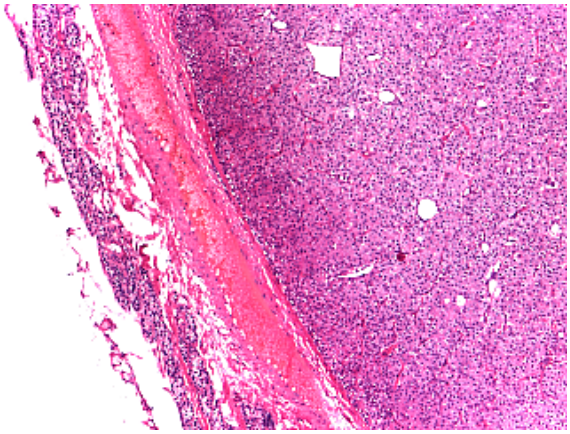


Figure 42. Parathyroid adenoma (right) with a rim of normal tissue (left), HE staining, x 40

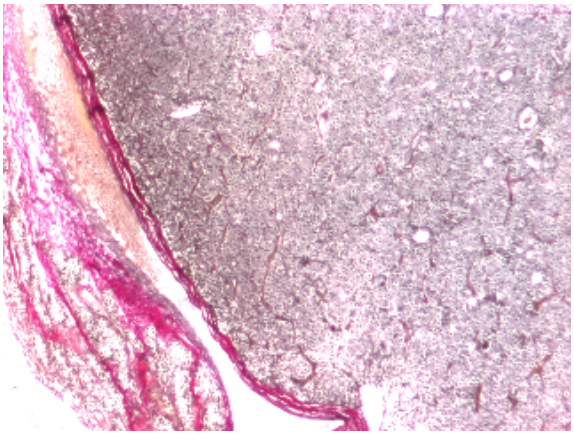


Figure 43. Parathyroid adenoma with a rim of normal tissue (left), van Gieson staining, x

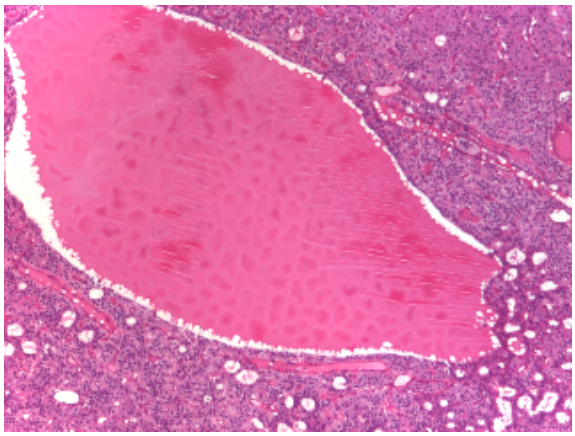


Figure 44. Solid sheets with focal acinar pattern and isolated cystic spaces, HE staining, x 40

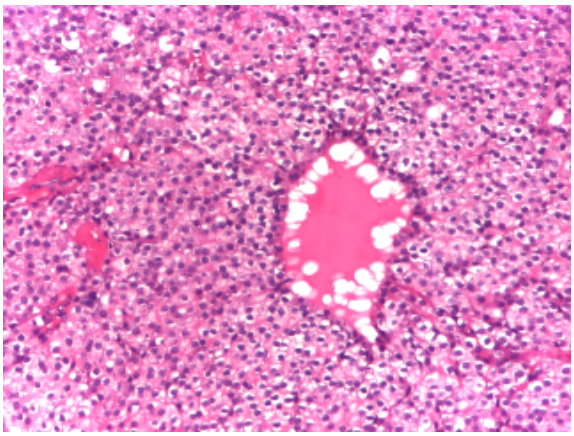


Figure 45. Cystic spaces with eosinophilic material, HE staining, x 100

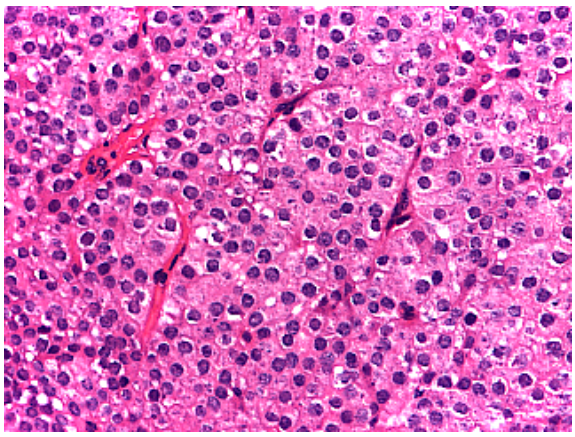


Figure 46. Chief cells with a pale eosinophilic cytoplasm and round nuclei, HE staining, x 200

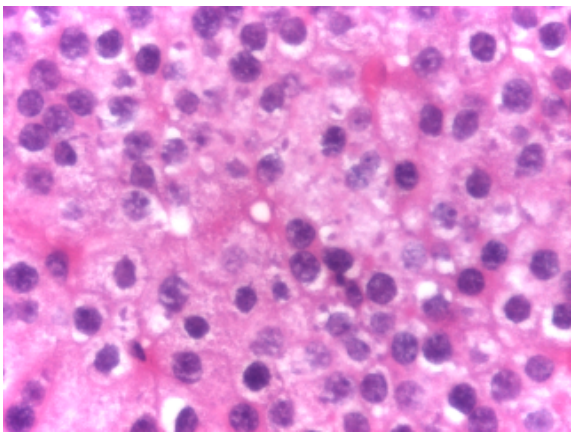


Figure 47. Chief cells with a pale eosinophilic cytoplasm and round nuclei, detail, HE staining, x 400

1.4.4. Discussions

On the basis of serum calcium levels it does not seem possible to predict hypocalcemia with clinical symptoms and the need for calcium–vitamin D supplementation because a significant statistical difference in terms of area under the curve between patients with asymptomatic hypocalcemia and patients with symptomatic hypocalcemia was not observed (Toniato et al., 2008).

The most commonly associated intervention with permanent hypocalcaemia is total thyroidectomy (2 cases, 50% of cases of permanent hypocalcaemia), interventions associated with one case being total thyroidectomy with selective neck dissection and totalization of thyroidectomy with radical dissection of the neck. Transient hypocalcaemia

was most commonly associated with simple total thyroidectomy (3 out of a total of 16 cases, 18.75%).

Two cases were recorded following total thyroidectomy accompanied by tumour excision, unilateral thyroidectomy with radical neck dissection, total thyroidectomies with radically modified dissection of the neck and enlarged total thyroidectomies.

One case was recorded as a consequence of total thyroidectomy with selective dissection, extended thyroidectomy with radically neck dissection and tracheostoma, and total thyroidectomy with radical dissection and definitive tracheostomy.

The predominance of female gender encountered in international and national literature is verified in terms of statistics of the 4th Surgery Unit in 2012-2018.

There are important international studies that highlight the differences in the rate of complications between different centers and operating teams, underlyening the importance of evaluating post-operative complications in the same center over a period of time. This is explained by the direct correlation between the risk of complications and the expertise and experience of the operating team (Fitzgerald, 2013; Nixon et al., 2013; Brandt et al., 2013).

Another study of our research center, between 2000-2002 revealed a complication rate of 6.87%. The studied group comprised all stages, including stages I and II, while the present study examines the complications of Stages III and IV . Also, the percentage of patients that required post-operative reintervention was reported to be 3.17%, while only 2 cases (1.72%) were documented in the present study. Permanent hypoparathyroidism was reported in 7.93% of patients, superior to the 3.44% found in this group. Considering these aspects, it appears that the experience of the operative team has contributed to the decrease of the rate of postoperative complications.

In a multicenter prospective study focused on the relationship between the rate of postoperative complications (recurrent lesion and hypoparathyroidism) and the experience of the operating team, an association has been found between the experience of the operating team and the surgical performance in thyroid cancer surgery, in the sense that the complications were the most common in the case of surgeons at the beginning or, on the contrary, at the end of their careers. Graves disease significantly increased the risk of transient lesion of the recurrent lacrimal nerve and transient hypoparathyroidism and could be a predictive factor for recurrent postoperative nerve damage and hypoparathyroidism after total thyroidectomy. From this point of view, better results were obtained because of the reducing of their complications rate (Duclos et al., 2012; Guo et al., 2013; Kisakol et al., 2003).

Regarding the correlation between surgical intervention and the frequency of postoperative complications, it can be seen that total thyroidectomy with the radical neck dissection and tracheostomy has involved most complications strictly related to the operative act. The patient who underwent this treatment had postoperative hypopharyngeal fistula, transient hypocalcaemia and bleeding, all these requiring reintervention. These complications also correlate with the stage and type of cancer, the patient presenting an IV C grade, thyroid anaplastic carcinoma with a diameter of approximately 15 cm, with right internal jugular vein thrombosis and a right subclavian vein thrombosis and direct invasion of the subhyoid muscles, cervical vessels and recurrent bilateral laryngeal nerve (Sitges-serra et al., 2010; Thomusch et al., 2003; Weetman et al., 1990).

Another type of intervention with multiple postoperative complications was extensive total thyroidectomy with radical neck dissection, in which the patient presented both complications directly related to the operative act and other complications: respiratory insufficiency and acute renal insufficiency. The patient had a fourth-degree papillary cancer with multiple comorbidities.

Routine administration of calcium vitamin D for two weeks was performed in all patients with total thyroidectomy, preventing symptomatic hypocalcaemia. The dose used was 3g per day 3 times a day in the first week and 1.5g three times a day in the second week. If symptoms of hypocalcaemia persist, it is recommended to supplement with intravenous calcium gluconate, one ampoule every 12 hours, for 7-10 days under the control of serum calcium. Hypoparathyroidism is considered permanent if calcium supplementation is still needed, more than 6 months after surgery. For patients with hoarseness, an indirect laryngoscopy was programmed at 1, 3 and 6 months postoperatively, respectively, until the vocal cords function. After 6 months recurrent paralysis is considered permanent (Shore and Waghorn, 2011; Wilhelm et al., 2016; Cui et al., 2019).

Furthermore, as outpatient thyroidectomy becomes increasingly common, it is important to develop maximally sensitive screening tools to identify patients that may need closer observation such as a 23 hour observation admission. While the utilization of PTH has been well studied in recent years, the inclusion of clinical factors should not be overlooked (Tuggle et al., 2011).

Depending on the postoperative progression, patients are usually discharged from the hospital in 2-3 days postoperatively after removing the drainage tube, this being done when the drained liquid does not exceed 20 ml for two consecutive days. Patients with various postoperative complications had a longer hospitalization period, depending on the complication and the solution to solve it (Christou et al., 2013; Cozzolino et al., 2004; Bergenfelz et al., 2008).

Follow-up after initial surgery is performed in the Endocrinology Clinic, whrere are done further investigations: a local clinical examination, dosing of serum TSH levels, leukoglobulin or calcitonin, depending on the type of cancer, and cervical ultrasound at 6-12 months, depending on the patient's risk for recurrence. The ultrasound should include the thyroid lodge and the central and lateral lymph nodes. If a positive result (ultrasound ganglia larger than 5/8/5 - 8 cm diameter) is highlighted, it is done a biopsy with a fine needle for cytology with tireglobulin dosing.

The annual incidence of the disease is estimated at approximately 0.2% of patients over 60 years age and the prevalence is estimated to be 1% or more due to the presence of a large number of asymptomatic non-diagnosed patients (Christou et al., 2013).

Clinical manifestations in some patients have been discrete and the disease has evolved in a benign manner for many years.

In rare cases, we noticed that the disease suddenly started or suddenly worsened, with patients experiencing severe complications. Thus, 11 cases presented severe dehydration and coma, the so-called hypercalcemiant parathyroid crisis. This disease has been more common in adults, with an apex of incidence between decades three and five, but may also appear in children or in elderly.

In approximately 20% of the patients we observed the hyperfunction of all parathyroid glands, constituting the clinical entity called parathyroid hyperplasia of the chief cells. Most of these last conditions are hereditary and are associated with other endocrine abnormalities. Some surgeons and anatomopathologists have reported that the increase in volume of several glands is common.

We have encountered hereditary hyperparathyroidism without other endocrine disorder, but more frequently it is part of a multiglandular endocrinopathy.

Patients with type I syndrome (MEN 1. Wermer syndrome) have hyperparathyroidism associated with pituitary and pancreatic tumours, frequently accompanied by peptic ulcer and gastric hypersecretion (Zollinger-Ellison syndrome).

Patients with MEN 2A syndrome have hyperparathyroidism associated with pheochromocytoma and medullary thyroid carcinoma. The way of transmission of both syndromes is autosomal dominant. For patients with MEN 2A syndrome, family screening was performed to identify the first degree relatives in risk of developing the disease.

In genetic malformations in MEN 1 and MEN 2A syndromes, cytogenetic studies of tumor tissue from patients with solitary adenomas have shown that at least two molecular defects are involved in the hyperparathyroid site: increased activity of a protooncogene or growth promoting gene and loss of functionality of a growth control gene (Lemmens et al., 1997; Erickson et al., 1999).

Adenomas are located more frequently in the lower parathyroid gland, but in 10% of patients parathyroid adenomas are located in the thymus, thyroid, pericardium or posterior wall of the esophagus. Adenomas weigh an average of 0.5-5 g, but we also encountered adenomas with the weight of 10-20 g. The adenoma is sometimes encapsulated by a crown of normal tissue.

In the case of the chief cells hyperplasia, the increase in the size of the glands can be asymmetric, so that some glands may seem normal at first view. In the presence of hyperplasia, the histological examination shows a normal appearance of the main cells and a loss of adipose tissue, even in the absence of glandular mass growth. Therefore, the microscopic examination of biopsies from multiple glands has proven to be essential for the interpretation of preoperative findings (Milas et al., 2003; Arnold et al., 2002).

In the presence of an adenoma, the other glands are usually normal, with a normal distribution of all cell types and with normal fat content.

Parathyroid carcinoma is generally less aggressive. Long-term survival without relapse is the rule if the initial intervention removes the entire gland without the capsule section and hemithyroidectomies (Grimelius et al., 2004; Schneider et al., 2014; O'Connel et al., 2011). Even in case of a relapse parathyroid carcinoma has a slow increase, with local extension to the neck. Treatment of disease recurrence remains possible. Rarely, parathyroid carcinoma is more aggressive, with distant metastases (lung, liver and bones) discovered at the initial intervention (Snover and Foucar, 1981; Vargas et al., 1997; Albright et al., 1934; Carneiro et al., 2004).

It is difficult to see if a primary tumour is carcinoma or not. An increasead level of mitotic images and the degree of fibrosis of the glandular stroma can mark the invasive character. Diagnosis of carcinoma is often retrospective. Hyperparathyroidism caused by a parathyroid carcinoma is not clinically different from other forms of primary

hyperparathyroidism (Biskobing, 2009; De Lellis, 2004; Sandelin et al., 1994). However, the high degree of calcium can correct the diagnosis.

Relative parathyroid insufficiency seems to be the principal mechanism of post-thyroidectomy hypocalcemia, even in patients with normal postoperative PTH concentrations.

The principal, and probably the only mechanism underlying postthyroidectomy hypocalcemia is parathyroid gland injury related to intraoperative trauma. A significant decrease (>50%) in PTH after surgery in patients with normal 4-hour PTH concentrations, is an independent predictor of postthyroidectomy hypocalcemia, implying that parathyroid injury after intraoperative trauma. It confirms previous observations that PTH concentrations within the normal range after TT do not exclude parathyroid insufficiency (Promberger et al., 2011).

These finding are of utmost importance, because they have both speculative and practical implications. From a speculative point of view, when reporting complications of thyroid surgery, surgeons should refer to hypoparathyroidism or parathyroid insufficiency, rather than hypocalcemia, which is only the effect of the parathyroid gland injury, the "true" surgical complication. This complication may be absolute when postoperative PTH is below the normal range (hypoparathyroid patients) or relative, when postoperative PTH concentrations are significantly lower than the preoperative (PTH ≥ 50%) and are not able to maintain normal postoperative calcium concentrations (Promberger et al., 2011).

The biochemical thresholds to indicate hypocalcemia are largely variable in the literature and this contributes to the wide variation in the report of postthyroidectomy hypocalcemia. Referring to parathyroid function as evaluated by PTH measurement, allows to better define and report such complication of thyroidectomy. In order to this it is recommended to obtain both preoperative and postoperative PTH concentrations in patients undergoing bilateral thyroid resection and to refer to absolute parathyroid insufficiency (hypoparathyroidism) when postoperative PTH concentrations are below the normal range and to relative parathyroid insufficiency when postoperative PTH concentrations are reduced by >50% after thyroidectomy, but still within the normal range of the laboratory (Edafe et al., 2014).

The practical implication is related to the postoperative management of patients who underwent thyroidectomy (Raffaelli et al., 2016).

The results of the histological study show that the parenchyma of the parathyroid gland is affected in both cases of investigated tumors. This is based on highlighting the morphological changes that occur in peritumoral that affect the functionality of the gland.

Postoperative hypomagnesaemia is not an independent predictor of hypocalcemia. It seems to be unnecessary to routinely measure the magnesium levels before and after thyroid surgery (Wang et al., 2017).

Further studies with larger cohort of patients, however, will be needed to further delineate the significance of the addition of clinical factors to this screening algorithm for symptomatic hypocalcemia.

1.4.5. Conclusions

An important postoperative complication of total thyroidectomy is given by hypocalcemia. This one can determin severe symptoms and also increases hospitalization time. The primary cause is secondary hypoparathyroidism following damage to, or

devascularisation of, one or more parathyroid glands during surgery. The present study can be continued with further researches in order to improve and develop surgical, oncological and endocrine management protocols for patients diagnosed with advanced thyroid cancerand to to avoid these relatively frequent and important complications.

We have also noted that primary hyperparathyroidism is three times more common in women than in males, being twice as many cases in patients older than 55 years as among the youngest. The most common forms are sporadic, which are based on genetic determinism or are associated with other endocrinopathies. Our study needs to be thorough in terms of clinical follow-up and genetic testing of a larger number of subjects. The obtained results encourage us to continue the research and, at the same time, we must point out that there is a high percentage of undiagnosed people among the apparently healthy population.

1.5. SURGICAL APPROACH OF NON-TUMORAL ENDOCRINE LESIONS IN CHILDREN

1.5.1. Introduction

Nodular goiter is a rare condition in pediatric populations, occurring in only 0.2%–5% of this category. Compared with adults, thyroid nodules are more frequent malignant in children and the incidence of this malignancy seems to be increasing (Jang et al., 2018).

Thyroid nodular disease contains a large spectrum of disorders including: unique nodular goiter, multinodular goiter, Hashimoto thyroiditis with nodularisation, Graves' disease with nodularisation. In children with thyroid autoimmune disorders we should beware because a neoplastic lesion may be small and undetectable at clinical examination. The diagnostic circumstances of thyroid nodules are different; they may be discovered during a physical examination or during the ultrasound of the neck (Niedziela, 2006).

New cases of thyroid cancer in people under the age of 20 represent 1.8% of all thyroid malignancies diagnosed in the United States. In adolescents between 15 and 19-year old, thyroid cancer is the eighth most frequently diagnosed cancer and the second most common cancer among girls. The adolescents have a 10-fold greater incidence than younger children to present thyroid cancer and the most affected are the girls (female to male ratio is 5:1) (Francis et al., 2015).

In children clinical findings that increase the likelihood of thyroid cancer are: male gender, history of external radiation to the head and neck or exposure to nuclear irradiance, rapid growth of goiter, a firm or fixed thyroid nodule, hoarseness or dysphagia (Fageeh, 2014).

Papillary and follicular thyroid cancer in childhood and adolescence is more advanced upon presentation than in adults. The recurrence rate is also higher in the young age. The survival in children and adolescents is better than in adults. An increase in the incidence of thyroid cancer has been observed in children exposed to the fallout of the Chernobyl accident (Nadyrov et al., 2012) especially in the age group of less than one year at the time of the explosion (Fageeh, 2014).

The pathological classification of differentiated thyroid cancer in children is based on standard definitions set by the World Health Organization (WHO). Papillary thyroid carcinoma accounts for 90% or more of all childhood case. Follicular thyroid cancer is uncommon like as medullary thyroid carcinoma or anaplastic thyroid carcinomas which are very rare in pediatric population. There are many histological variants of pediatric papillary thyroid carcinoma all having a distinctive set of nuclear characteristics. Subtypes of papillary thyroid carcinoma are: classic, solid, follicular, and diffuse sclerosing (Francis et al., 2015).

Factors suggesting the malignant thyroid nodule in children and adolescents are: prior exposure to internal radiation, ultrasound features of malignancy, cold nodule on scintigraphy, malignant cytology on fine needle biopsy aspiration and positive biomarkers of malignancy in aspirates (BRAF mutation, ret/PTC, RAS mutation) (Niedziela, 2006).

Considering the particularities of thyroid carcinoma in children and adolescents we have investigated the prevalence of thyroid carcinoma among the thyroid disorder emphasizing on the surgical treatment in terms of indication, methods and complications.

1.5.2. Materials and methods

We investigated the medical records of 35 patients (children and adolescents) admitted with diagnosis of nodular goiter at Endocrinological and Surgical Departments, St. Spiridon Hospital, Iasi, Romania, between 2011-2018. Demographic data (sex/age), thyroid ultrasonographic features, fine needle biopsy aspiration, hormonal profile, surgical treatment procedure as well as histological aspects were recorded.

Thyroid ultrasound and fine needle aspiration biopsy (performed only in patients with *Thyroid imaging reporting and data system* "TIRADS" score of 4 or 5) were done by well-trained endocrinologists and fine needle aspiration biopsy specimens were reviewed by qualified pathologists. The results of fine needle biopsy aspirations were recorded in compliance with Bethesda classification. The surgical treatment was performed by experienced surgeons in the field of thyroid nodular disorders.

Serum thyroid stimulating hormone (TSH), free T4 (fT4), calcitonin, Serum anti-thyroid peroxidase antibody (TPOAb) and thyroid stimulating hormone receptor antibody (TRAb) were measured. The reference values were as follows: TSH 0.51-4.30 μUI/mL, fT4 0.97-1.67ng/dl, TPOAb <20 mUI/ml, TRAb<1.75 UI/L, calcitonin 9.82pg/ml.

Each medical record contain written informed consent of the parents or legal guardian.

1.5.3. Results

The retrospective study included the medical records of 26 (74%) girls and 9 (26%) boys (**Figure 48**) with a mean age of 11.66 years, most patients being in age group of 11 (6 patients), 15 (7 patients) and 16 (8 patients) years old (**Figure 49**).

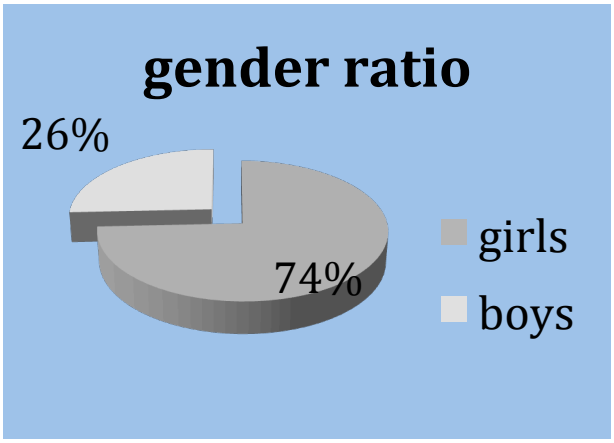
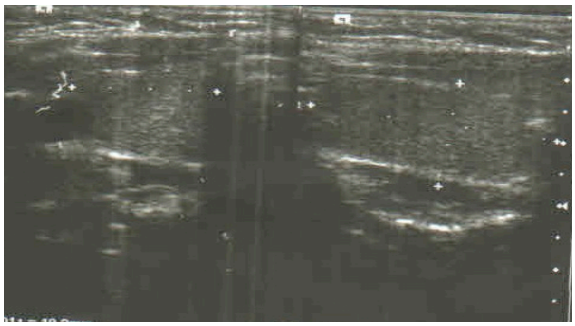


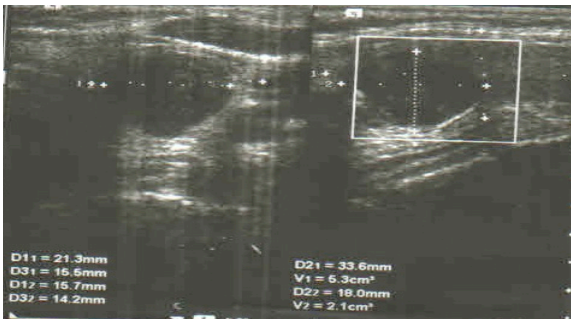
Figure 48. Female /male ratio in the study group.

Figure 49. Age stratification according with the number of patients for each age group

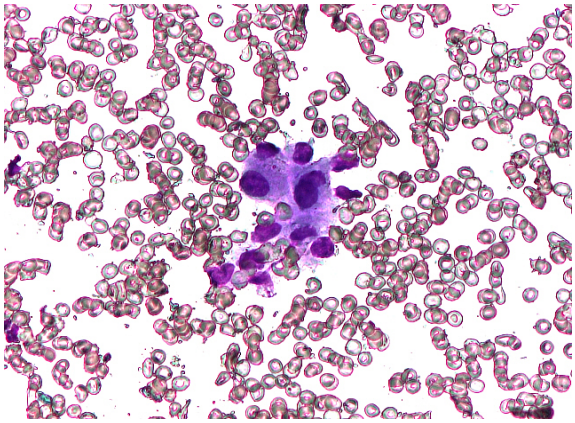
The thyroid ultrasound examination revealed: unique micronodule (< 1cm) of the left lobe in 3 patients, unique micronodule of the right lobe in 2 patients, multiple micronodules in both lobes in 3 patients, unique macronodule (> 1cm) of the left lobe in 4 patients, unique macronodule of the right lobe in 5 patients, multiple macronodules in both lobes in 3 patients, unique microcyst of the left lobe in 4 patients, unique macrocyst of the left lobe in one patient, nodules with suspicious features of malignancy (TIRADS 4 or 5) in 7 patients, multiple micronodules in large, hypoechogenic thyroid with hypervascularisation in Doppler mode in 3 cases (**Figure 50**).



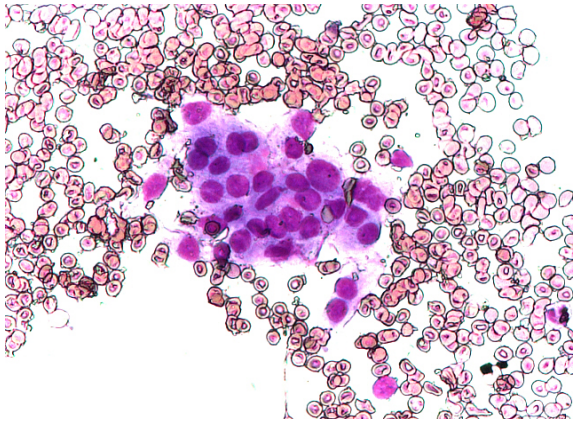
a.



b.



c. Thyrocytes with enlarged nuclei



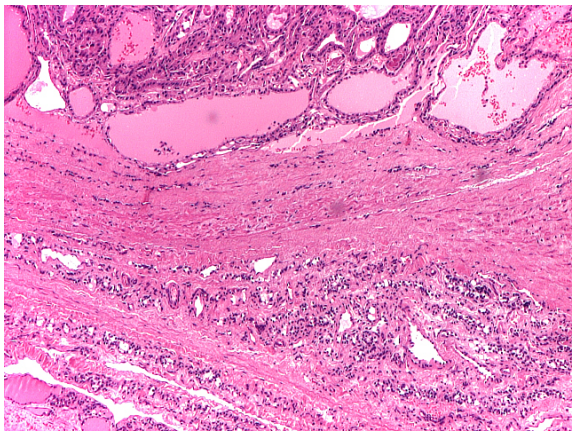
d. Thyrocytes with hyperchromatic, unequal nuclei

Figure 50 a.b. Polynodular goiter, with moderate dysplasia**. c.d.** Hystological aspects after fine needle aspiration biopsy

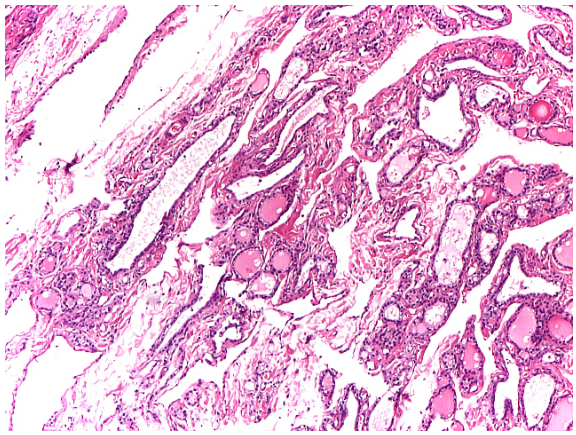
Fine needle aspiration biopsy was performed in 10 cases due to the TIRADS score ≥ 4 with Bethesda II in 3 cases, Bethesda III in 4 cases and Bethesda V in 3 cases (**Figure 50 c, d**).

The thyroid function was normal (euthyroidism) in 29 cases (82.8%), abnormal in 6 cases (17.2%), thyrotoxicosis in 4 cases and hypothyroidism in 2 cases (**Figure 51**). All patients with one exception had normal values of calcitonin. The presence of TPOAb in high titers was mentioned in 2 patients (Hashimoto thyroiditis) and of TRAb in two patients (Graves' disease).

The surgical treatment was performed in 16 (45.7%) cases due to fine needle aspiration biopsy results or due to the relapse after medical treatment in cases with hyperthyroidism (**Figure 52, a, b**). Lobectomy was performed in 7 (43.7%) cases while total thyroidectomy was the final option for the rest of 9 (56.3%) patients (**Figure 53**).

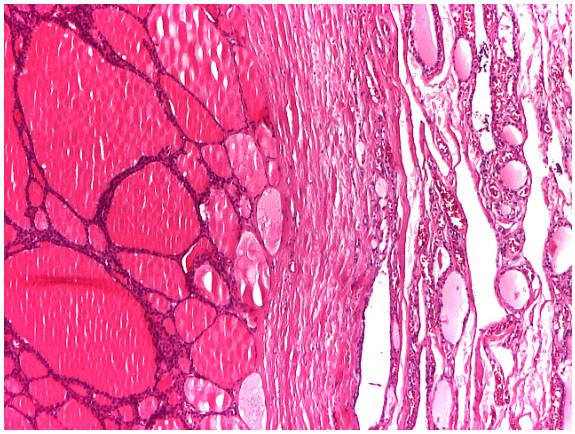


a. Macrofollicular adenoma

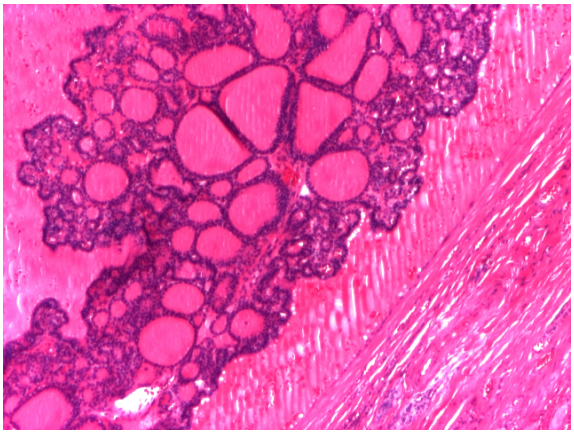


b. Extranodular area with hypofunction

Figure 51. Nodullar goiter, 12 yers old



a. Colloid goiter with adenomatous macrofollicular nodule, HE, x 4



b. Adenomatous nodule with area of hyperfunction and capsular sclero-hialinosis, HE, x 4

Figure 52. Nodular goiter 2 months evolution, 11 years old.

The treatment option (medical or surgery) was made in accordance with the thyroid function (euthyroidism, hyperthyroidism or hypothyroidism) and clinical, ultrasound and fine needle biopsy aspiration findings (**Table 15**).

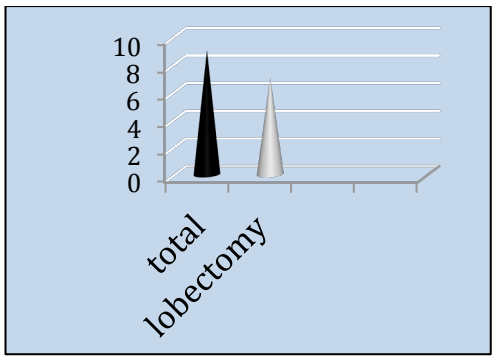
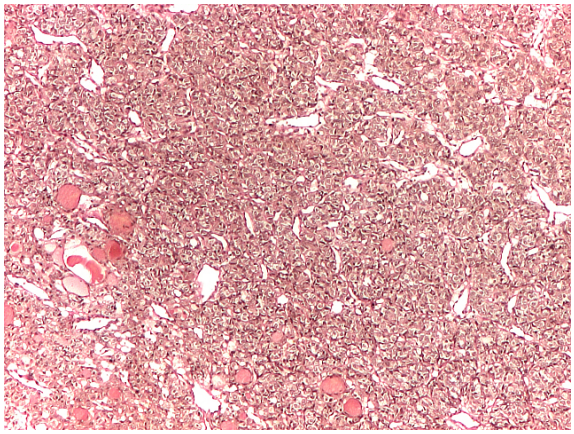
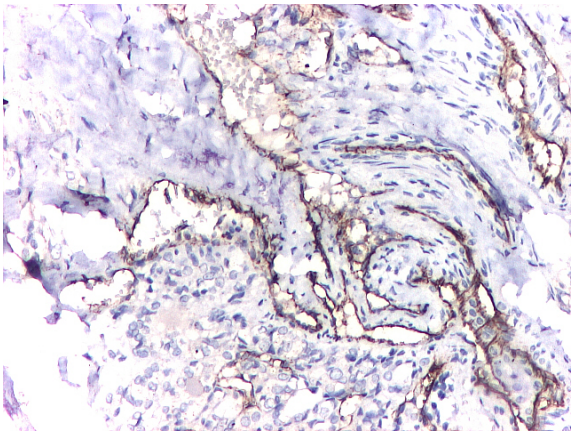


Figure 53. Total thyroidectomy vs lobectomy in pediatric population with surgical treatment for nodular thyroid disorders.

In the group of 16 patients submitted to surgery as a result of pathological examination in 8 cases the thyroid carcinoma has been found (**Figure 54 a,b**). The rest of 8 patients presented benign thyroid findings (follicular adenoma, toxic adenoma and Graves' disease with follicular adenoma) (**Table 16**).



a. Microfollicular and trabecular areas VG, x 4



b. Intravascular tumor emboli, CD31, x 10

Figure 54. Nodular goiter, Follicular carcinoma, 1 year evolution, pT3aN0 G1 L0V1 Pn0
14 years old.

The prevalence of thyroid carcinoma among the pediatric population with thyroid nodules was 22.8% (**Figure 55**) most affected being the female gender. In our study group no complication after surgical treatment was present. The post-surgical evolution was normal with discharge in 2-3 days after the procedure.

Table 15. Therapeutical options according with the thyroid function.

TREATMENT	**HYPERTHYROIDISM**	**HYPOTHYROIDISM**	**EUTHYROIDISM**
SURGERY	3 cases (total thyroidectomy)	-	6 cases (total thyroidectomy) 7 cases (lobectomy)
DRUGS	-	2 cases (l-thyroxine)	-
NO TREATMENT	-	-	16 cases
OTHER	1 case (ethanol sclerosis)	-	

Table 16. Pathological profile of the nodular goiter in children and adolescents submitted to surgery.

PATHOLOGY	No. cases
Benign	**8**
Follicular adenoma	6
Graves disease + folicullar adenoma	1
Toxic adenoma	1
Malignant	**8**
Follicular carcinoma	1
Graves' disease + papillary carcinoma	1
Papillary carcinoma	4
Medullary carcinoma (MEN type 1b)	1
Well differentiated tumor of uncertain malignant potential	1

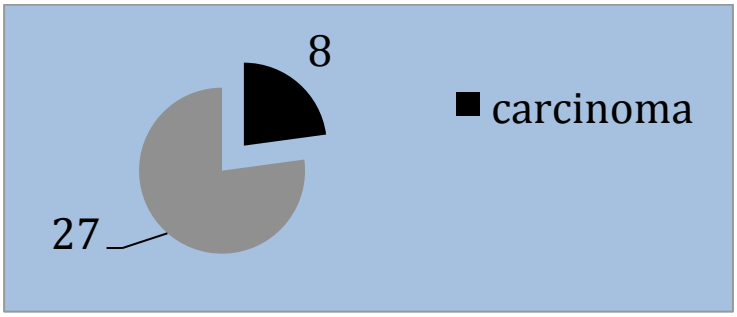


Figure 55. Number of patients with thyroid malignancy among those with nodular disorders.

1.5.4. Discussions

Our results show a prevalence of 22% of thyroid malignancy among pediatric population with thyroid nodular disorders. This incidence is comparable to the reported prevalence of thyroid cancer in pediatric thyroid nodules of 20%–26%. In Korea, the childhood thyroid cancer prevalence is 18% and the incidence increased 3 fold from 1999 to 2012 (0.5/100,000 to 1.7/100,000) and in the United States and the United Kingdom, the incidence of thyroid cancer in pediatric populations also appears to be increasing (Jang et al., 2018). In fact, thyroid cancer is the most common pediatric endocrine cancer of all childhood malignancies.

The mean incidence of thyroid carcinomas in childhood thyroid nodules which were operated shows an overall 26.4% risk of cancer. If in adults, women to men ratio is 4: 1, in children below 15 the ratio of girls to boys is 1.5:1 and in patients aged between 15-20 years the female to male ratio is 3:1. Males and children under 10 years are at higher risk of cancer. Age is also the major determinant of recurrence in pediatric differentiated thyroid carcinoma, particularly in those younger than 10 years (Niedziela, 2006).

In a study conducted in the United States, thyroid nodules were present in 1.8% of school children between the ages of 11 and 18 years. The incidence of thyroid carcinoma in children is reported to be approximately 1.75 per 100,000 (Fageeh, 2014).

Well-differentiated thyroid cancers are the most common endocrine tumours in children and adolescents. A significant increase in the incidence of thyroid cancers was observed in children following the nuclear reactor meltdown in Ukraine and those exposed to the atomic blasts in Japan (Nadyrov et al., 2012; Radetti et al., 2019).

Screening for papillary thyroid carcinoma in children at risk is, however, an issue of debate. It is important to mention that thyroid nodules in children are five times more likely to be malignant than in adults. Pediatric and adolescent papillary thyroid carcinoma is possible to have no relationship with gender in prepubertal children, while after puberty; girls are 4–5 times more prone to have thyroid cancer than boys (Palaniappan et al., 2018).

The incidence of thyroid cancer is higher in children presenting with nodular goiter compared with adults. In children, thyroid nodules have been reported to be malignant between 9.2% and 50% whereas in adults, the incidence of thyroid cancer is between 5% and 15% (Palaniappan et al., 2018).

The majority of malignant nodules are found in a uninodular goiter. Follicular adenoma is the most frequent nonmalignant diagnosis in children with thyroid nodules. The distribution of malignancy in pediatric goiter is similar to that seen in adults. Papillary thyroid carcinoma is the most frequent malignancy among children with nodular thyroid disorders (Palaniappan et al., 2018).

Risk factors for developing thyroid nodules in pediatric population include: female gender, iodine deficiency, head and neck irradiation, age of puberty, and family or personal history of thyroid disease. Several diseases as: abscesses, lymphatic or vascular malformations, ectopic thymus, thyroglossal duct cysts, and tumors can mimic thyroid nodules in children (Palaniappan et al., 2018). The risk of thyroid neoplasia in children is elevated at any radiation dose (Guille et al., 2015). Another risk factor for thyroid malignancy in pediatric population is the Hashimoto thyroiditis. *In children this autoimmune disorder can be accompanied by important thyroid structural alterations. In time period benign thyroid nodules, carcinoma and, rarely, primary non-Hodgkin lymphoma can develop. However, the relationships between HT and neoplasm are poorly defined.* The frequency of papillary thyroid carcinoma in children and adolescents with Hashimoto thyroiditis was found from 0.67 to 3% (Penta et al., 2018).

Papillary thyroid cancer and follicular thyroid carcinoma present major clinical differences in terms of uni- or multinodular presentation, lymph nodes metastasis and hematogenous metastases. Hematogenous metastases to the lungs occur in up to 25% of cases and generally occur only with significant regional lymph node metastases in papillary forms. A unifocal tumor and hematogenous metastases to lungs and bones are specific for the follicular type (Francis et al., 2015).

In order to decide the necessity of surgery multiple modalities are employed to help characterize thyroid nodules (ultrasound, radionuclide scans, fine needle aspiration biopsy, and thyroid function tests). Even all these tests are also performed in the pediatric population; these patients frequently undergo partial or total thyroidectomy for diagnosis (Khozeimeh et al., 2011). An ultrasound examination to determine the main characteristics in term of: volume, structure, vascularisation is always necessary. Some authors have tried to define a set of characteristics that identify nodules at a higher risk of malignancy: the ultrasound evaluation of thyroid nodules- the Thyroid Imaging Reporting and Data System (TIRADS) (Pompili et al., 2018).

If feasible, given the patients age and anxiety level, a fine needle aspiration biopsy should be performed (Khozeimeh et al., 2011). As biomarkers, circulating tumor cells from solid tumors can predict metastases and prognoses are helpful after the surgical treatment in order to monitor the treatment efficacy (Qiu et al., 2018).

The surgical excision is the only option in those patients who have an inadequate or malignant fine needle biopsy aspiration or in cases when this procedure was not performed. Total thyroidectomy remains the procedure of choice for those lesions identified preoperatively as cancer, while lobectomy should be employed for those lesions in which the diagnosis is uncertain (1 Khozeimeh et al., 2011).

Because most pediatric patients with thyroid pathology are adolescents, they are frequently operated on by general surgeons or endocrine surgeons in medical centers for

adults as well. The approach varies from country to country and depends on the general principles of the medical care system in a given region (Baglaj et al., 2013).

Surgical resection remains the "gold standard" of management for all children and adolescent with thyroid carcinoma but there is still controversy regarding the extent of resection. Pediatric population with papillary thyroid carcinoma, not undergoing a total thyroidectomy, is at a higher risk for developing recurrences. The relative high incidence of multifocal disease is an argument for a total thyroidectomy in pediatric papillary thyroid carcinoma. A central neck dissection should be performed when there is evidence of central and/or lateral neck metastasis or gross extra thyroidal invasion (Palaniappan et al., 2018).

The post-surgical complication rate according different authors is 22%, including permanent recurrent nerve damage in 6.2% and permanent hypoparathyroidism in 12.3%. Complications can be minimized by the surgeons who perform thyroid surgeries at the high-volume centers (Palaniappan et al., 2018).

The thyroid cancer in pediatric population is a challenge for the endocrinologist as well for the surgeon. The majority of pediatric patients with nodular goiter who have the indication of surgical treatment are operated by the general surgeon who must have a great experience in the field of thyroid surgery. The expertise in thyroid surgery is necessary in order to have a curative treatment and to avoid postoperative complications. A close collaboration is needed between pediatrician, endocrinologist and surgeon for children with thyroid cancer in order to receive proper and effective treatment.

1.5.5. Conclusions

Surgical treatment of nodular disorders in children must be performed after a careful clinical examination and tests that accurately establish the existence of a possible malignant proliferative process. Even the nodular goiter is a rare event in pediatric population the risk of thyroid carcinoma is increased that way the extent of surgical removal of the thyroid is very important. The total thyroidectomy and radical neck dissection must be performed only in specific cases when the results of fine needle biopsy aspiration are illustrative for malignancy.

1.6. NEW-EDGE PENCHANTS ON NEOPLASIA PREDICTIVE MODELS

1.6.1. Introduction

A particular interest in modern medicine is given to prevention and prognosis of malignant tumours. This is one of our basic concerns in the case of thyroid and parathyroid cancers.

The 8th edition of the American Joint Committee on Cancer (AJCC) staging system has significantly updated the classification for cancer-nodemastasis (TNM) significantly in thyroid cancer. This provides better predictability of survival and recurrence. The eighth

edition of the AJCC TNM staging was concerned with patients diagnosed with thyroid papillary carcinoma, resulting in better predictability of recurrence and, implicitly, survival compared to the previous staging system (AJCC, 2018).

If a screening protocol can not be applied and the risk population can not be identified it is necessary to establish criteria for early diagnosis and patients management. With regard to thyroid cancer, recent studies show the utility of genetic tests to detect oncogenes involved in thyroid tumorogenesis (Chisholm, 2009; Alzahrani, 2013; Song, 2018).

Endocrine surgery and modern oncology explore new methods of early diagnosis of thyroid and parathyroid cancers. They should be minimally invasive, cost-effective and widely applicable. Our research focuses on advanced radiological techniques combined with protocols mathematical analysis formulas for captured images.

Thus, modern MRI and fMRI equipment acquires high resolution and quality images that can be analyzed quantitatively and qualitatively. The capacity of dosing peptide, lipid or RNA molecules is an absolute novelty in our area of interest (Celli, 2018).

It has recently been demonstrated as feasible the use of fractal statistics for the characterization and synthesis of medical images. Traditionally, global fractal dimensions based on morphological coverings have been used to quantify the texture of sampled data sets. This texture could be used to describe second order statistics in 2D magnetic resonance imaging or microscopic images.

With the benefits of fractal analysis, the need for faster and more efficient computational algorithms has emerged Range Over Standard Deviation, Experimental Trend Analysis (ROSETA) is an algorithm that brings significant improvements to computational performance by calculating fractal statistics based on entropy instead of morphological geometric statistics. ROSETA can be used as a robust analytical tool for general purposes. Literature describe several examples of its implementation (Jaenisch, 1994).

There is also a simple variation of this algorithm that facilitates manual calculation using a computer. This simple calculation can be used to analyze blood pressure, temperature and heart rates as selected time samples with very few total points (Jaenisch, 1994).

The dynamics of complex systems, from functionality and structure points of view, lead to some instabilities. These instabilities involve either chaos (noise regeneration) or pattern generation (interference, diffraction fields, etc.). In classical concepts, the theoretical models (hydrodynamic, kinetic) are built, assuming that the dynamics of the complex system's structural units occur on continuous and differentiable motion variables (energy, momentum, density, etc.), exclusively dependent on spatial coordinates and time. In reality, the complex system's dynamics are much more complicated and the classical theoretical models failed in the attempt to explain all these aspects, as illustrated by experimental observations (Badii, 1997; Mitchell, 2009; Chen, 1994; Morozov, 2012).

These difficulties can be overcome with a complementary approach, using fractal concepts, which were defined for the first time by Mandelbrot. He introduced the term "fractal" to describe the "exotic" shapes that did not fit the patterns of Euclidean geometry, i.e., irregular geometrical objects, cells of living organisms, human arterial vessels, neural networks, the convoluted surface of the brain, which possess invariance with respect to the scale transformations. This approach is considered an extension of the conventional Euclidean geometry (Mandelbrot, 1982).

Entropy Kolmogorov is an important measure that describes the degree of chaos of the systems. It gives the average loss of information about a basic point position on the attractor. Numerically, Kolmogorov entropy can be estimated as Rényi entropy. A special case of Rényi entropy is the theory of information about Shannon's entropy. The product of Shannon entropy and the Boltzmann constant is thermodynamic entropy. Fractal structures are characterized by their fractal dimension. There is an infinite family of fractal dimensions. A generalized fractal dimension can be defined in a dimensional space. Rényi entropy and the size of the generalized fractal are linked by a straight relationship (Zmeskal, Dzik, P. et al., 2013).

Shannon's concept of entropy was introduced in 1948 (Shannon, 1948). It is a measure of the average information content when the value of the random variable is not known. Typically, Shannon entropy is defined by the following expression S (X) = - logbΣi = 1mpilnpi where X is a discrete random variable, pi is the event probability {X = xi}, and b is the basis of the logarithm used.

In information theory, Rényi entropy is, in fact, a generalization of Shannon entropy. It is one of the functional families to quantify the diversity, uncertainty or randomness of a system (Rényi, 1970). The entropy of the Rényi order is defined for (as a limit) by the equation where it is a discreet random variable, is the probability of the event and is the basis of the logarithm.

Entropy Kolmogorov offers great advantages by proposing a new theory of complexity. According to this theory, the complexity of a message is given by the size of the program needed to allow the reception of message. From these ideas, Kolmogorov analyzes eg. the entropy of literary texts (Pushkin's poetry). This entropy seems to be a function of the semantic capacity of the texts, depending on factors such as their extension and also the flexibility of the corresponding language (Garrido, 2011).

In this spirit, fractal analysis has proven to be a useful tool describing various systems from physics, chemistry, biology, medicine (Cattani, 2016; Hastings, 1993; Falconer, 2003).

Moreover, the analysis of complex systems evolution showed that most of them are non-linear and, therefore, new mathematical tools were required. These have been provided by the scale relativity theory (SRT) and by the extended scale relativity theory (ESRT), the SRT with an arbitrary constant fractal dimension (Guariglia, 2016; Nottale, 2003).

These theories consider that the motions of the complex system’s structural units take place on continuous but non-differentiable curves (fractal curves). In this situation, the Euclidean dynamics of a complex system subjected to external constraints is replaced by fractal dynamics characterizing the same system, but free of any external constraints. More precisely, the constrained motions in the Euclidian space, i.e., on continuous and differentiable curves, are substituted by free, independent motions (without constrains) in a fractal space, i.e., on continuous, but non-differentiable (fractal) curves. Therefore, non-differentiability becomes a fundamental property of the complex system’s dynamics. In such a conjecture, a correspondence between the interaction processes and the non-differentiability (fractality) of the motion trajectories can be established (Merches, 2016).

Then, for specific scales that are large with respect to the inverse of the highest Lyapunov exponent, the deterministic trajectories are replaced by a collection of potential trajectories, while the concept of definite positions is substituted by that of the probability

density. Moreover, the complex system's structural units may be reduced and identified with their own trajectories so that the complex system will behave as a special fluid lacking interactions (via their geodesics in a fractal space). Let us call such a fluid a "fractal fluid". In the present paper, the role of fractal entropy in the pairs generating processes is analyzed. The general theory and some applications are also discussed (Hillborn, 1994, Cristescu, 2008).

Although it is a theoretical study, it has extensive practical implications in the field of endocrine surgery, oncology and radiology. The purpose of this study is to develop a theoretical model for the applicability of the fractal analysis concept in current medical practice in order to achieve an early diagnosis protocol of thyroid malignancies.

Evaluation by fractal analysis of the variations of the two forms of serum cholesterol brings indirect and quantifiable information on thyroid function.

At the same time, this model can be applied to another non-differentiated system model with increased specificity on thyroid and parathyroid function evaluation.

1.6.2. Materials and methods

This study is about applicability of fractal entropy theory and non-differentiated models. In this regard, we conducted this study on a human biological structure - cholesterol, under its two forms: HDL and LDL. We used the Shennon entropy calculation formula. We applied it to this non-differentiated model of the two circulating serum cholesterol subtypes.

We selected this molecule because it is present in most human tissues and, by presenting the two circulating forms, it can be part of the category of non-differentiated Lye models, evaluated based on the Hamiltonian variation formula.

1.6.3.Results

All the equations used in this study are related to **Table 17** (from E1 to E33).

In such a framework, some consequences of non-differentiability, both in the usual space (of the space and time coordinates) and in the scales space, are evident:

- ✓ any continuous but non-differentiable curve of the complex system's structural units (fractal curve) is explicitly dependent on scale resolution δω, its length tends to infinity when δω tends to zero;
- ✓ the physics of the complex system phenomena is related to the behavior of a functions set during the zoom operation of the scale δω. Then, through the substitution principle, δω will be identified with dω, δω = dω. Consequently, it will be considered as an independent variable;
- ✓ the complex system dynamics is described through fractal variables, functions dependent both on the space-time coordinates and the scale resolution, since the differential reflection invariance in relation to ω, of any dynamical variable, is broken.

As consequence, the velocity field, both in the usual space and in the scales space, becomes a complex variable dynamic, with the form of E1, where the real part, Vl D, is the differentiable velocity and the imaginary one,Vl F, is the non-differentiable (fractal) velocity; the differential of the spatial coordinate field, d±Yi, both in the usual space and in the scales

space, is expressed as the sum of two differentials, one of them being the differential part d±yi and the other one being the scales fractal part - E2.

The sign "+" corresponds to the forward process, while the sign "−" to the backward one;

- ✓ the fractal part of the spatial coordinate field, both in the usual space and in the scales space, satisfies the fractal equation E3, where DF defines the fractal dimension of the fractal motion curve and λi± are constant coefficients that indicate the fractalization type;
- ✓ an infinite number of fractal curves can be found relating any pair of points, both in the usual space and in the scales space. Then, any external constraint is interpreted as a selection of fractal curves, both in the usual space and in the scales space, and the real curves, corresponding to the maximum of the probability density;
- ✓ the complex system dynamics, both in the usual space and in the scales space, can be described through a covariant derivative as E4 and E5.

In the previous relations the indexes l, k take the values1, 2, 3 in the usual space, while in the scales space they have an arbitrary dimension imposed by the intrinsic structure of the complex system. Thus, this operator plays the role of the covariant derivative, namely it is used to rewrite the fundamental equations of complex system dynamics, both in the usual space and in the scales space, in the same form as in the classic (differentiable) case.

Under these conditions, applying the operator to the complex velocity field, in the absence of any external constraint and for motions on Levy curves, which implies the restriction of E6, where λ is the fractal-nonfractal transition coefficient, considered with "+" for dωi0 and with "−" for dωh0 has the following form of E7.

Previous results show that, both in the usual space and in the scales space, the local "acceleration", the "convection" and the "dissipation" make their balance at any point of the non-differentiable curve.

Moreover, the presence of the complex viscosity-type coefficient indicates that the complex system is a rheological medium. For irrotational motions, the complex velocity field ∧ Vi takes the form of E8.

Then substituting this relation in Equation (7), the geodesics equation, both in the usual space and in the scales space, becomes E9.

In the previous Equations above, lnΨ is the scalar potential of the complex velocity field. As the geodesics Equation is of a fractal Schrödinger type, the function Ψ, through ρ = |Ψ|2, becomes a density probability, thus motivating the procedure for deterministic trajectories substitution with "potential trajectories collection", the probability densities.

If Ψ = √ρexp (iS) with √ρ is the amplitude and S is the phase of Ψ, the complex velocity field has the real part in E10 and the imaginary one in E11.

Substituting first Equation with the $10^{th}$and 11^{th} in 7^{th} Equation and separating the real and the imaginary parts, up to an arbitrary phase factor which may be set to zero by a suitable choice of the phase of Ψ, we obtained E12, where Q is the specific fractal potential is ilustrated by E13 and E14.

Equation twelve represents the specific momentum conservation law, while the E13 represents the states density conservation law. These equations define the fractal hydrodynamical model both in the usual space and in the scales space.

This may be seen clearly from the absence of this velocity from the states density conservation law. Any interpretation of the specific fractal potential should take cognizance of the "self" nature of the specific momentum transfer. While the standard energies are stored both in the form of the mass motion (kinetic energy) and potential energy, some is available elsewhere and only the total energy is conserved. It is the conservation of the total energy and momentum that ensures "fractal reversibility" and the existence of the fractal eigenstates, but denies a Levy motion fractal force of interaction with the "fractal medium".

Fractal Entropy through Non-Differentiable Lie's Group Working with a variant of the Schrodinger-type geodesics equation (see E9), it implies that to each dynamic variable Θi, a fractal operator can be associated ∧ Θi. This leads us to fractal differential equations with eigenfunctions and eigenvalues. For example, the fractal operator of the angular momentum is given by the equation E15, where ∧ r, ∧ P are the fractal position-type and, specific momentum-type (the momentum of the mass unit) operators, respectively. Thus, the E15 becomes E16.

These non-diferentiable operators satisfy the Lie fractal algebra - E17 and they make invariant the norm of the null vectors - E18.

It can be shown, in a "strange" manner, that the operators satisfy the same algebras as Pauli's matrices - E19, E20, E21, E22. The infinitesimal operators and do not tell us very much about this group. In this respect, we shall set operators in a form capable of putting into evidence its isomorphism to known groups.

The new operators are given by the linear combinations in E23.

Taking α and α as group variables and admits the solution F = constant therefore, we can take F = 1. Thus, the group is measurable, having as an elementary measure - E24 - where "∧" represents the external products of the diferential 1-forms dα and dα. According to the Jaynes observations, if there are unspecified circumstances that admit this group of invariance, then the equally probable situations a priori accept a uniform distribution of the elementary measure given by dM in E25.

Further, we will illustrate such an unspecified circumstance as a direct result of considering a canonic formalism. Indeed, the fact that our Lie's group in the space of null vectors makes invariant the elementary measure dM shows that it is, equally, a simplectic group.

The corresponding Hamiltonian dynamics is generated in the tangent space by the vectors ∧ O1, ∧ O2, ∧ O3, that satisfy the commutation relations. A general vector is a linear combination of the form - E26.

A problem arises: finding the functions that are invariant along the trajectories tangent to this vector, the solutions of the equations - E27.

Taking into consideration the E24, it can be explicitly written as E28.

The characteristic differential system of this equation has the form of E29 and admits the first integral in E30.

Therefore, the solution will be an arbitrary function of this expression that has a particular role in the theory, namely that of the Hamiltonian that generates the motion. Indeed, the differential system is the Hamilton's associated system equations in E31, in which case α is a coordinate - type variable and α a momentum-type one. We noted with dτ the common value of the two differentials.

The differential of the affine parameter on the integral curves of the vector. Deriving relations with respect to the affine parameter τ and eliminating α and α based on E30, the symmetric equations are obtained in E32.

In principle, among the solutions is, also, the density of the complex Gaussian probability expressed as E33, where statistical significances can be associated with parameters μ, λ and ν.

Table 17. Equations used in this study to quantify the fractal entropy of cholesterol

NUMBER	EQUATION FORMULA
E1	$\hat{V}^i = V_D^i - iV_F^i,\ i = \sqrt{-1}$
E2	$d_\pm Y^i = d_\pm y^i + d_\pm \sigma^i$
E3	$d_+\sigma^i(\omega, d\omega) = \lambda_\pm^i (d\omega)^{1/D_F}$
E4	$\frac{\hat{d}}{d\omega} = \partial_\omega + \hat{V}^l\partial_l - \frac{1}{4}(d\omega)^{(2/D_F)-1} D^{lk}\partial_l\partial_k$
E5	$D^{lk} = \left(\lambda_+^l\lambda_+^k - \lambda_-^l\lambda^k\right) - i(\lambda_+^l\lambda_+^k + \lambda^l{}_-\lambda^k{}_-)$ $\partial_l = \frac{\partial}{\partial Y^l};\ \partial_l\partial_k = \frac{\partial^2}{\partial Y^l\partial Y^k}$
E6	$\frac{\hat{d}\hat{V}^i}{d\omega} = \partial_\omega\hat{V}^i + \hat{V}^l\partial_l\hat{V}^i - i\lambda(d\omega)^{(2/D_F)-1}\partial^l\partial_l\hat{V}^i$
E7	$\frac{\hat{d}\hat{V}^i}{d\omega} = \partial_\omega\hat{V}^i + \hat{V}^l\partial_l\hat{V}^i - i\lambda(d\omega)^{(2/D_F)-1}\partial^l\partial_l\hat{V}^i$
E8	$\hat{V}^i = -2i\lambda(d\omega)^{(2/D_F)-1}\partial^i ln\Psi$
E9	$\lambda^2(d\omega)^{(4/D_F)-2}\partial^l\partial_l\Psi + i\lambda(d\omega)^{(2/D_F)-1}\partial_\omega\Psi = 0$
E10	$V_D^i = 2\lambda(d\omega)^{(2/D_F)-1}\partial^i S$
E11	$V_F^i = \lambda(d\omega)^{(2/D_F)-1}\partial^i \ln\rho$
E12	$\partial_\omega V_D^i + \left(V_D^l\partial_l\right)V_D^i = -\partial^i Q$
E13	$\partial_\omega\rho + \partial^i\left(\rho V_D^i\right) = 0$
E14	$Q = -2\lambda^2(d\omega)^{(4/D_F)-2}\frac{\partial^l\partial_l\sqrt{\rho}}{\sqrt{\rho}} = -\frac{V_F^l V_{Fl}}{2} - \lambda(d\omega)^{(2/D_F)-1}\partial_l V_F^l$
E15	$\hat{L} = \hat{r}\times\hat{P} = -i\lambda(dt)^{(2/D_F)-1}\left(\hat{r}\times\nabla\right)$
E16	$\hat{M}_1 = -i\lambda(dt)^{(2/D_F)-1}\left(Y_2\frac{\partial}{\partial Y_3} - Y_3\frac{\partial}{\partial Y_2}\right)\ \hat{M}_2 = -i\lambda(dt)^{(2/D_F)-1}\left(Y_3\frac{\partial}{\partial Y_1} - Y_1\frac{\partial}{\partial Y_3}\right)$ $\hat{M}_3 = -i\lambda(dt)^{(2/D_F)-1}\left(Y_1\frac{\partial}{\partial Y_2} - Y_2\frac{\partial}{\partial Y_1}\right)$
E17	$\left[\hat{M}_1, \hat{M}_2\right] = i\lambda(dt)^{(2/D_F)-1}\hat{L}_3\ \hat{M}_2 = -i\lambda(dt)^{(2/D_F)-1}\left(Y_3\frac{\partial}{\partial Y_1} - Y_1\frac{\partial}{\partial Y_3}\right)$ $\hat{M}_3 = -i\lambda(dt)^{(2/D_F)-1}\left(Y_1\frac{\partial}{\partial Y_2} - Y_2\frac{\partial}{\partial Y_1}\right)$
E18	$Y_1^2 + Y_2^2 + Y_3^2 = 0$
E19	$Y_1 = \rho\sin\omega,\ Y_2 = -\rho\cos\omega,\ Y_3 = -i\rho$
E20	$\hat{M}_1 = \cos\omega\cdot\rho\frac{\partial}{\partial\rho} - \sin\omega\cdot\frac{\partial}{\partial\omega}\ \hat{M}_2 = \sin\omega\cdot\rho\frac{\partial}{\partial\rho} + \cos\omega\cdot\frac{\partial}{\partial\omega}\ \hat{M}_3 = -i\frac{\partial}{\partial\omega}$
E21	$v_+ = \sqrt{\rho}e^{\frac{i\omega t}{2}},\ v_- = \sqrt{\rho}e^{-\frac{i\omega t}{2}}$
E22	$\begin{bmatrix}\hat{M}_1 & v_+\\ \hat{M}_1 & v_-\end{bmatrix} = \frac{1}{2}\begin{bmatrix}0 & 1\\ 1 & 0\end{bmatrix}\begin{bmatrix}v_+\\ v_-\end{bmatrix}\begin{bmatrix}\hat{M}_2 & v_+\\ \hat{M}_2 & v_-\end{bmatrix} = \frac{1}{2}\begin{bmatrix}0 & i\\ -i & 0\end{bmatrix}\begin{bmatrix}v_+\\ v_-\end{bmatrix}$ $\begin{bmatrix}\hat{M}_3 & v_+\\ \hat{M}_3 & v_-\end{bmatrix} = \frac{1}{2}\begin{bmatrix}-1 & 0\\ 0 & 1\end{bmatrix}\begin{bmatrix}v_+\\ v_-\end{bmatrix}$
E23	$\hat{L}_1 = \hat{M}_1 - i\hat{M}_2,\ \hat{L}_2 = \hat{M}_3,\ \hat{L}_3 = -(\hat{M}_1 + i\hat{M}_2)$
E24	$\hat{O}_1 = \bar{\alpha}\frac{\partial}{\partial\alpha},\ \hat{O}_2 = \frac{1}{2}\left(\alpha\frac{\partial}{\partial\alpha} - \bar{\alpha}\frac{\partial}{\partial\bar{\alpha}}\right),\ \hat{O}_3 = -\alpha\frac{\partial}{\partial\bar{\alpha}}$
E25	$\left[\hat{O}_1, \hat{O}_2\right] = \hat{O}_1,\ \left[\hat{O}_2, \hat{O}_3\right] = \hat{O}_3,\ \left[\hat{O}_3, \hat{O}_1\right] = -2\hat{O}_2$
E26	$\hat{T} = \mu\hat{O}_1 + 2\nu\hat{O}_2 + \lambda\hat{O}_3$
E27	$\hat{T}H(\alpha,\bar{\alpha}) = 0$
E28	$(\nu\alpha + \mu\bar{\alpha})\frac{\partial H}{\partial\alpha} - (\lambda\alpha + \nu\bar{\alpha})\frac{\partial H}{\partial\bar{\alpha}} = 0$
E29	$\frac{d\alpha}{\nu\alpha + \mu\bar{\alpha}} = -\frac{d\alpha}{\lambda\alpha + \nu\bar{\alpha}} = d\tau$
E30	$H(\alpha,\bar{\alpha}) = \frac{1}{2}\left(\mu\bar{\alpha}^2 + 2\nu\alpha\bar{\alpha} + \lambda\alpha^2\right)$
E31	$\frac{d\alpha}{d\tau} = \frac{\partial H}{\partial\bar{\alpha}} = \nu\alpha + \mu\bar{\alpha},\ \frac{d\bar{\alpha}}{d\tau} = -\frac{\partial H}{\partial\alpha} = -\lambda\alpha + \nu\bar{\alpha}$
E32	$\ddot{\alpha} + (\mu\lambda - \nu^2)\alpha = 0\ \ \ddot{\bar{\alpha}} + (\mu\lambda - \nu^2)\bar{\alpha} = 0$
E33	$P(\alpha,\bar{\alpha}) = \frac{1}{\sqrt{\mu\lambda - \nu^2}}\exp(-H)$

In this framework, in **Figure 56** we present the states density ρ = ΨΨ for this system, where Ψ is the complex conjugate of Ψ determined from E9 for the stationary case, while in **Figure 57** the associated informational entropy is shown.

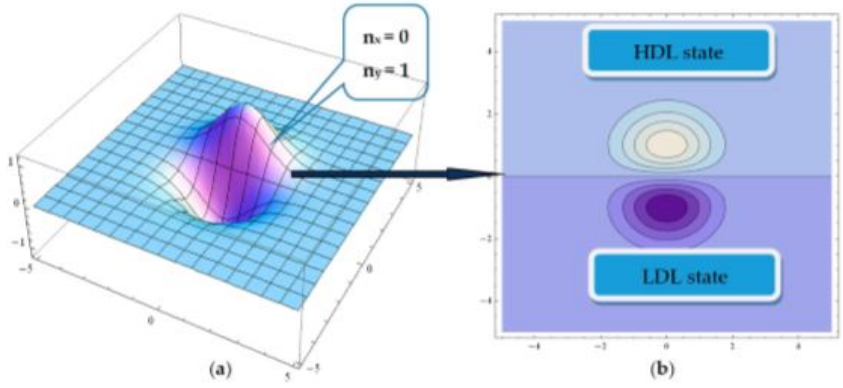


Figure 56. The states densities ρ = ΨΨ of the two-dimensional harmonic oscillator: three-dimensional (a); and contour plot (b) dependences, associated with the LDL-HDL pair induced by the quantum numbers nx and ny

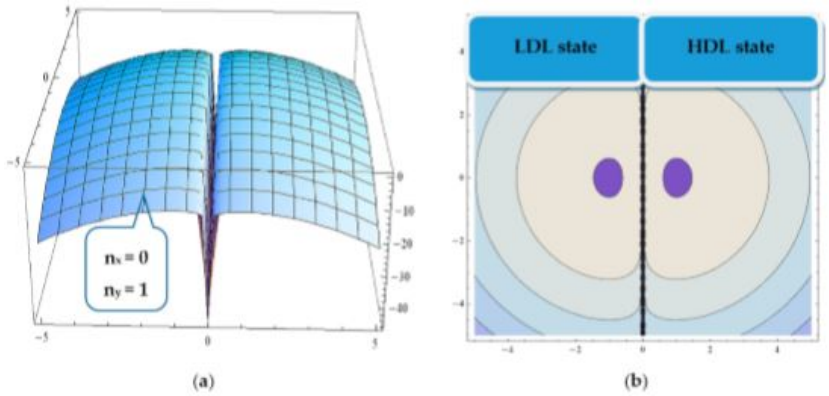


Figure 57. The informational entropy
ρ ln=I : three-dimensional (a); and contour plot dependences (b) associated with the LDL-HDL pair induced by the quantum numbers n_x and n_y

1.6.4. Discussions

Analysis of fractal dimension and entropy Shannon has recently been used in several areas of medicine, such as cardiology, neurology, ophthalmology and radiology (Arruda, 2013, Moreira, 2011) and are useful in characterizing irregular and complex structures, using fractal analysis. Recent studies have correlated the degree of differentiation and tumour invasiveness in prostate cancer and the degree of rejection of cardiac tumors (Keipes, 1993; Karperien, 2008; Oliveira, 2014).

Considering the functionality of a generalized covariance principle (the complex system physics laws are in variant both with respect to space-time transformation sand to the scales ones), the transition from the classical physics of complex system dynamics to the non-differentiable (fractal) one can be implemented by replacing the standard derivative operator d/dω with the non-differentiable operator ∧ d dω (Mandelbrot, 1982; Cattani, 2016; Hastings, 1993).

Recent studies reported results of the applicability of fractal analysis in translational medicine. The hemagglutinin sequences of the H1N1 virus from different strains were classified with fractal size values of the correlation matrix comprised in the use of a DNA representation via the Voss indicator function (Voss, 1992; Cattani, 2010).

Multifractal properties of mRNA variants of multiple myeloma were established at a 1.26 fractal size convergence by generating DNA patterns with wavelet analysis that reveal hidden symmetries (Cattani, 2008, 2012, 2012).

A new hypothesis that high fractal dimension sequences may be upper-level regulators (transcription factors) was recently discussed in the ENCODE project. This needs further investigation (Gerstein, 2012). Other hypotheses (although not the main concern in translational medicine) could include the high fractal sequence as the regulator for microbe

bioelectricity (Lovley, 2011), the optimal sequence of fractal dimensions for photosynthesis genes involving quantum transport (Panitchayangkoona, 2011; Smyth, 2012; Thilagam, 2012).

This fact may confirm, from a mathematical point of view, the idea from statistical fractal mechanics, according to which the complex probability density must be, also, a movement integral.

From such a perspective, the non-linear interactions between the structural units of the complex system induce a "fractal medium"; therefore, every structural unit is in a perpetual "interaction" with the "fractal medium" (Nottale, 1993, 2011; Merches, 2016).

The "fractal medium" dynamics are described by the fractal hydrodynamics equations, by the momentum and states density conservation laws. The specific fractal potential is, at the same time, both a measure of the interaction degree between the structural unit and the fractal medium, as well as of the motion curves fractality. The fractal velocity field does not represent actual motion, but contributes to the transfer of the specific momentum and energy (Nottale, 1993, 2011; Merches, 2016).

Since our Lie's group in the space of null vectors is isomorphic to the Barbilian group, it results that the complex Gaussian Equation, with additional constrains, can have the role of an entropy in a fractal theory of motion.

This method, called Incremental Fractal Entropy of Diversity (FEID), is based on information entropy and increasing diversity.

Then, a new method of positioning the nucleosomes is provided by using the FEID in the dataset of diverse DNA sequences of human subjects (Heintzman, 2007; Li, 2001).

Experimental results show that FEID is an efficient method of positioning nucleosomes as compared to other methods. Finally, the most important nucleotide sequence in nucleosome positioning is provided based on the calculated contribution rates of the nucleotide sequences(Zuo, 2010).

Since nucleosomal positioning is of great importance in telemedicine, genetic variations in the distant area will be found fast, when combining information on the positioning of nucleosomes with biological processes,. In addition, gene diagnosis will be determined rapidly in the future (Lu, 2010, Chen, 2010, 2012, Ioshikhes, 1996).

Pairs Generating Mechanisms: Implications in Dynamics of Biostructures Schrodinger-type fractal dynamics implies the functionality of the "states entanglement" for the structural units of a complex system, and, implicitly, their "monogamy" (Nottale, 2011; Merches, 2016).

For example, the electron with a spin value of +1/2 is entangled with the electron with a spin value of −1/2, generating the Cooper pairs from superconductivity. Also, the neutron and the proton are entangled, generating the pair from superfluidity. At another scale, high density lipoproteins (HDL) and low density proteins (LDL), the two forms of cholesterol, entangle and generate the "structural unit" of cholesterol-type (Nottale, 2011; Merches, 2016).

The fact that these two forms are entangled is confirmed by the *"chameleon-like"* behavior of cholesterol, confirmed by different medical experiments. For example, Van Lenten found that HDL taken from the same subjects before and after an acute phase behaved differently: before, HDL prevented the mild oxidation of LDL, while the same concentrations

of HDL taken during the acute-phase response were not as effective in preventing lipid hydroperoxide formation. Moreover, the HDL taken during the acute phase actually enhanced LDL-induced monocyte migration. This, together with other experiments performed by van Lenten, support the concept that unlike LDL, HDL is chameleon-like, changing its colors (apoproteins and associated enzymes) as the landscape changes (going from the basal state to the acute-phase response and back to the basal state), if HDL protection is largely due to its ability to inhibit or destroy the biologically active lipids in LDL, the changes in HDL induced by the acute-phase response could result in an increase in the local modification of LDL (Van Lenten, 1995).

In such a context, in order to describe the dynamics for HDL and LDL cholesterol, presented above, we will use the Schrödinger-type representation in the E9 for the stationary case, which can be viewed as a fundamental equation of biological structures morphogenesis. *It has not been yet considered as such, because its unique domain of application was, up to now, the microscopic* (molecular, atomic, nuclear and elementary particle) domain, in which the available information was mainly about energy and momentum (Cattani, 2016; Hastings, 1993).

However, our fractal model extends the potential domain of applications for Schrödinger-type equations to every system in which the three conditions (an infinite or very large number of trajectories, afractal dimension of individual trajectories, local irreversibility) are fulfilled. Macroscopic Schrödinger equations can be constructed, not based on Planck's constant, but on constants that are specific to each biological structure and may emerge from their self-organization.

Indeed, considering that both LDL and HDL are two different states of the same "entity", cholesterol in the form of a LDL-HDL pair, the dynamics of such a biological structure can be described, for example, by means of a harmonic oscillator with a plane symmetry.

The informational entropy is given by the logarithm of the same polynomials; we note that these polynomials are solutions of the E9 for the stationary case and for plane symmetry (Cattani, 2016; Hastings, 1993; Agop, 2016).

It can be seen that such a pair (HDL-LDL) "operates" in a state of maximum informational entropy (Merches, 2016; Agop, 2014).

In order to overcome the difficulties generated by the fact that the classical theories failed in explaining the dynamics of real complex sytems, i.e., fluid and kinetic models in the study of some phenomena, such as combustion, drug delivery, solid components separation in mixtures, and plasma ablation behavior, the fractal concepts and the corresponding non-differentiable theoretical models can be applied. Thus, the fractal entropy through non-differentiable Lie groups, compatible with a Hamiltonian-type formalism, was established. Furthermore, the pairs generating mechanism was explained through fractal entanglement states.

We identified implications of the presented theory in the dynamics of some physical systems (the electron with a spin value of 2 1+ is entangled with the electron with a spin value of 2 1− , generating the Cooper pairs from superconductivity; the neutron and the proton are entangled, generating the pair from superfluidity) and biological structures (in the form of cholesterol).

1.6.5.Conclusions

Recently, telemedicine solutions have become a new trend in medical treatment. Many diseases result from abnormal variations in biological processes, especially in the positioning of nucleosomes. Thus, the actual prediction of nucleosome positioning becomes a hotspot in telemedicine research.

We assume that the applicability of this fracture analysis method evaluated for serum cholesterol is given by the possibility of performing the same type of analysis on RNA specific molecules and binding peptides, specific to the normal thyroid function. Thus, we are opening the way for a revolutionary early diagnosis method applicable to thyroid cancers and even parathyroid cancer. By applying fractal analysis techniques to high-performance radiology, it is possible a qualitative assessment of the target viscers.

2. ADVANCES IN DYGESTIVE SURGERY

2.1. STATE OF THE ART

The academic research in general surgery has started with my PhD thesis focused on chronic pancreatitis. My permanent concern in digestive surgery addresses both the upper and lower gastro-intestinal tract. This concerns relate to research of early diagnosis and treatment methods in chronic pancreatitis and colorectal cancers.

I have considered these two main topics within digestive surgery because colorectal malignancy is the most common cause of death in the male and third in the female after breast and cervical cancer. At the same time, chronic pacreatitis is a pathology with increased incidence in our country, which raises special problems of treatment and follow up.

The history of gastrointestinal surgery is marked by four distinctive aspects:

- major contributions to surgical technique were made by individual surgeons who were considered truly giants at that time; they carried out the transposition of scientific observations and knowledge of pathophysiology into patient care protocols.
- the evolution of the field was supported by the advances in the related fields: anesthesia and intensive care, radiology, gastroenterology and bioengineering; this type of patients require complex postinterventional care and specialized teams to be managed.
- the gastrointestinal surgery field has evolved without the benefit of organized and structured training programs; the need for specialized training in the complex gastrointestinal surgery area is becoming more and more appreciated, and it is likely that such training is more and more demanded.
- advances in the field of pharmacology and microbiology have had a profound effect both on the incidence and safety of surgical procedures and also recurrences.

Similarly, antimicrobial therapy has increased the safety of colic resection and other major operations (Mulvihill and Debas, 2008).

The introduction of clinical trials in gastrointestinal surgery research dates back less than 100 years ago. At the beginning of the 20th century lectures and textbooks were the primary source of information, the latter providing the only way to establish and communicate findings and progress in the field (Andreas and Kaiser, 2002).

In the same time prestigious surgery schools and their academic leaders began conceptualizing standardized surgical techniques we benefit today. Among the most important centers of the nineteenth century in Europe was the Vienna Medical School, where surgeon Theodore Billroth, chairman of the second surgery clinic, pioneered numerous innovations (Schonbauer, 1947).

At the same time, Eduard Albert, who was the president of the first Surgical Clinic in the same center, has established a remarkable reputation in the field by publishing his surgical manual. Its special volume of Emergency Surgery was one of the most important and most comprehensive material presentations published until that time (Albert, 1897-1898; Corman, 1989).

The performing of the gastrointestinal surgical sections, sutures and anastomosis are of general and historical interest, as it is prooved by the evolution of surgical techniques and scientific vocabulary (Lirici and Hüscher, 2016).

In this branch of general surgery, colorectal cancer surgery has a special place, assured by its particularities in prevention, early diagnosis, treatment and prognosis (Miles, 1971; Moynihan, 1908).

One of the major challenges of current screening programs is the still low acceptance of colonoscopy within the general population. Future strategies include raising patient awareness through healthcare providers, and improving alternative screening procedures, such as genetic testing or virtual colonoscopy (Lange et al., 2008).

One of the major advantages of colonoscopy is the endoscopically removing of polyps and the effectiveness of screening programs is influenced by the oncological frequency and safety of the preneoplastic lesion resection (Reguero and Longo, 2015).

According to current colorectal oncology guidelines, the curative potential of endoscopic resections for malignant tumours depends on the so-called high or low risk criteria, including data related to the age of the patients and the hereditary nature of the disease. In this context, submucosal endoscopic dissection (ESD) is limited to very few indications and its impact on morbidity is still low (Vitone, 2013).

However, the current direction of colorectal oncology surgery is for laparoscopic and conservative sphincter resections, with better acceptance among patients and physicians (Green et al., 2013).

The concepts of multimodal therapy for colorectal carcinoma include adjuvant chemotherapy, interventional and surgical hepatic metastases and systemic chemotherapy. All this contributes to a decreased mortality and improved survival. All activities aimed at reducing incidence, morbidity and mortality in colorectal cancers imply intense cooperation between gastroenterologists, oncologists, anatomopathologists, radiotherapists and surgeons (Bonjer, 2015; Fleshman, 2015).

The use of immunohistochemical markers in early diagnosis and staging of colorectal cancers is of particular importance in the management of these patients. Numerous studies have investigated the prognostic role of biomarkers values in the context of the colorectal

liver metastases, but without being introduced into routine clinical practice (Toren et al., 2018).

Biomarkers have been shown to be involved in multiple oncogene signaling pathways that control cell growth, apoptosis, angiogenesis and immune detection and include: Ki-67, EGFR, p53, hTERT, CD34, TSP-1, KISS1, Aurora kinase A and CDX2. CD34 and TSP-1 values are significantly associated with long-distance survival (Asghar et al., 2010).

Regarding the molecular landscape of the progress of colorectal carcinogenesis, new biomarkers with improved prognostic and predictive potential are discovered. Biological biopsy in fluid is a promising tool for real-time evaluation of tumour clonal evolution, response to therapy, presence of minimal residual disease and acquired resistance. The use of non-invasive biomarkers can lead to the molecular classification of tumours in real time and the individualization of the treatment of these patients (Zarkavelis et al., 2017).

Biomarkers are extremely useful in assessing the prognosis of patients with metastatic rectal cancer after their surgical or oncological cure (Toren et al., 2018; Siizu et al., 2019).

Increasing tumour aggressiveness is a negative prognostic factor for invasive colorectal cancer and can be assessed by immunohistochemical determination of cytokeratin. Recent studies have explored the optimal value for estimating lymph node metastases using cytokeratin immunohistochemistry and developed a computer assisted semiautomatic quantification method to reduce data variability (Takamatsu et al., 2019).

The introduction into the current medical practice of semiautomated software for the evaluation of immunohistochemical specimens of risk factors for metastatic lymph nodes provides predictable results.

I have focused my personal approach on studying colorectal cancers in the prospect of taking part in the conjugated effort to lower the incidence and increase the survival rate of patients diagnosed with this disease. My primary goal is to target immunohistochemical markers useful in early diagnosis of colorectal cancers and those with increased specificity in assessing the prognosis of patients.

I believe that the future of this research direction belongs to the correlation of the techniques and mathematical formulas of the fractal analysis of the immunohistochemical markers of neovasculogenesis with the advanced techniques of medical radiology.

In terms of chronic pancreatitis, current research directions are pointing on conservative treatment. Current choices for the diagnosis and treatment of chronic pancreatitis are unsatisfactory in terms of early detection and prevention of its progression. Most new and experimental therapies aim to limit inflammation and reduce pancreatic fibrosis. For this purpose, models on laboratory animals were developed on targets through which they were tested (Van der Gaag, et al., 2012).

Chronic pancreatitis is a disease that progresses slowly and meantime with the diagnosis of the patient it is necessary to be supported and trained to change their lifestyle. In order for symptomatic treatment, pain control should be carefully managed to prevent drug addiction and exocrine insufficiency. Also, diabetes mellitus should be strictly controlled to prevent its complications. These patients require a multidisciplinary approach to maximize the results of the treatment (Yadav et al., 2018; Kwon et al., 2019).

Progress on early diagnosis is due to the evolution of radiological techniques and, in particular, to MRI. The results obtained by this technique have been improved in order to

qualitatively assess the exocrine function of the gland by its hormonal stimulation - administration of secretin (Sanyal et al., 2012; Tirkes et al., 2013, 2019; Sherman et al., 2014; Mesel et al., 2014; Trikudanathan et al., 2015).

Over time, in the study of chronic pancreatitis, great help came from the etiopathogenic and treatment models performed on laboratory animals. The choice for the right model is difficult and the scientific reasoning has to be carefully analyzed. It depends on the purpose for which of the models of chronic pancreatitis are we looking for symptoms (Aoki et al., 2006; Vonlaufen et al., 2007).

Injections of chemical compounds that cause repeated pancreatic lesions are among the most commonly used models. The established protocols, the correct dose and the optimal injection interval must be established in the individual laboratory tests before each set of experiments (Aghdassi et al., 2011).

Features of chronic pancreatitis in human patients include multiple structural and functional characteristics that can be reproduced in animal models. Even so, no available animal model of chronic pancreatitis is known to replicate all of these features (Reed 2014; Foster 2014).

This research direction has been materialized by publishing the following articles:

1. **Grigorovici A,** Andronic D, Hînganu D, Hînganu MV, Varcus F. Enzymatis treatment of chronic pancreatitis. *Rev Chim Bucharest* 2019; 70(3):1014-1016.
2. **Grigorovici A**, Velicescu C, Hînganu D, Călin A, Hînganu MV, Andronic D. The use of neoprene in experimental pancreatitis. *Rev Chim Bucharest* 2019; 70(2):676-678.
3. Cobzeanu BM, Irimiciuc S, Vaideanu D, **Grigorovici A**, Popa O. Possible dynamics of polymer chains by means of Ricatti's procedure – an exploitation for drug release at large time intervals. *Materiale plastice* 2017; 54(3):531-534.
4. Hînganu D, Stan CI, Ciupilan C, **Grigorovici A**, Bulimar V, Dima-Cozma C, Hînganu MV. Anatomical and imunohistochemical evaluation of colorectal cancer. *Rev Chim Bucharest* 2019; 70(1):236-238.

2.2. PROGNOSTIC FACTORS IN COLORECTAL CANCERS

2.2.1. Introduction

Colorectal cancer is a malignant disease with high morbidity and mortality. Neoplastic growth is characterized by uncontrolled proliferation well above the apoptosis rate, as well as loss of cell differentiation. For this point of view a neoplasm means a cell growth disorder evidenced by excessive cellular proliferation. Determination of this proliferation can be used in the positive diagnosis and prognosis of neoplastic lesions, and from this point of view, Ki67 is a valuable marker because is not influenced by other comorbidities such as melitus diabetes, cardiovascular disorders, congenital malformations. Overexpression of this marker may suggest a disturbance of cell division, resulting in the

appearance of an intensely-growing tumor. The marker is also used to determine the degree of aggressiveness and the metastatic tumoral potential (McLeod and Murray, 1999; Jankowski et al., 2008).

The mechanisms by which Ki-67 is involved in cell cycle control are not fully elucidated, but there is a hypothesis that increased values of Ki-67 would act by inhibiting the cell cycle by inducing cellular self-stabilization (Jankowski et al., 2008).

Immunohistochemical markers CD-34 and Ki-67 appeared relatively recent in the studies. Both markers are sensitive to the assessment of tumor aggressiveness. In normal tissues are very low expressed, and abundant in tumoral tissues. Neoangiogenesis refers to the growth of new capillary vessels from those that already exist. These vessels are strictly orientated to the tumor. This phenomenon is necessary for the tumoral metastasis and, if it does not occur, it is not realized; there are studies on important batches of patients showing a relation of determinism between microvascular density and metastatic risk. The expression of these markers is correlated, in the same studies with the patients prognosis, being directly proportional to it. The same was observed in breast cancer, stomach cancer and brain cancer (Miettinen et al., 2005; Vieira et al., 2005; Nieto et al., 2007; da Silva et al., 2008; Li et al., Ma et al., 2010).

The data show that expressions of CD-34, Ki-67 markers are inversely proportional to the degree of tumor histologic differentiation and with tumor staging depending by degree of local extension. At the same time, it is widely accepted that angiogenesis processes have a determining role in the metastasis process and patient prognosis by fascial tunnels organized arround bloodvessels. These two immunohistochemical markers are of high sensitivity and precision, but, however, their expression can not play the role of organ diagnosis because they can not localize the tumor.

A 6-month, serial evaluation can play the role of a marker of cancer progression or regression and signifies a new tool in assessing the prognosis of these tumors.

The purpose of the study is to evaluate the immunohistochemical expression of the Ki-67 marker in colorectal adenocarcinomas. Intratumoral concentrations of the Ki-67 antigen are correlated with the tumour proliferation rate and thus the prognosis of the patients.

2.2.2.**Materials and methods**

The study was conducted on a group of 28 patients diagnosed with rectal cancer. We made the histopathological and immunohistochemical evaluation of patients in the study group. The evaluation was performed on the sections stained with hematoxylin-eosin, and for mucinous forms, on sections stained with Alcian blue. We selected the cases for the immunohistochemical examination, the techniques being applied to low differentiated colorectal carcinomas. Ki-67 is expressed throughout the cell cycle except for the G0 phase, which is why Ki-67's intratumor concentration values correlate with the tumor proliferation rate and thus the prognosis of the patients.

The nuclear accumulation of the Ki-67 protein was assessed semi-quantitatively: negative (-) which means lack of coloration or presence in less than half of the cells and positive (+) which means the presence of nuclear staining in over 50% of tumor cells. In turn,

the positive response was assessed low positive, moderately positive and strongly positive (+, ++ and +++).

2.2.3. Results

Most of the studied cases were moderate and low differentiated colorectal adenocarcinomas (G2 and G3). Approximately 60% were in advanced stages (T3), with perirectal adipose tissue invasion.

In G2 adenocarcinomas (**Figure 58**), tumor cells delineate glandular, irregular cavities sometimes with papillary excrescences of different shapes and sizes. The nuclei are large, elongated, hypercromatic, placed on 3-4 layers that occupy the entire thickness of the epithelium. There are areas of ulceration and infection with the presence of stromal inflammatory infiltrates.

In G3 adenocarcinomas, tumour cells are usually small with hyperchromic nuclei. The stromal volume is increased, there are frequent ulceration areas, the stromal inflammatory infiltrate being abundant (**Figure 59**).

Of all the cases of studied colorectal tumours, we considered mucinous carcinomas the cases where the mucinous component represented more than 30% (**Figure 60**).

Immunohistochemical exam in sections stained for Ki-67 has shown that the topography of reaction is strictly nuclear (**Figures 61, 62, 63**), but we could not accurately identify the nuclear localization depending on the division stage.

In the tumor there are Ki-67 poor stained areas, probably due to the completion of phase (interphase) and degradation of nuclear staining.

The lack of expression of studied markers in neighboring non-tumor tissues, including Ki-67, suggests that cancerous tissue proliferates in a pathway that is not correlated with adjacent tissues.

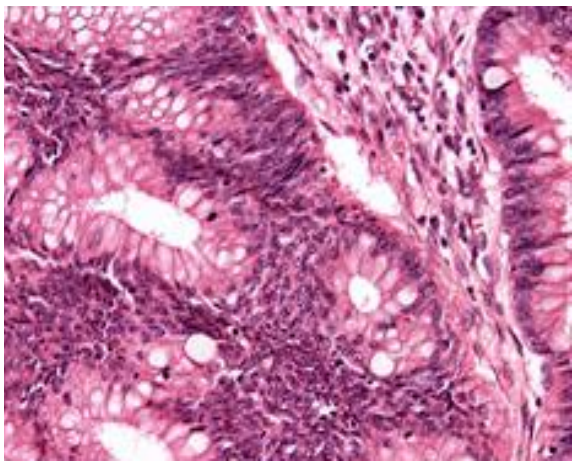


Figure 58. Moderately differentiated colorectal carcinoma. H & E staining, x40.

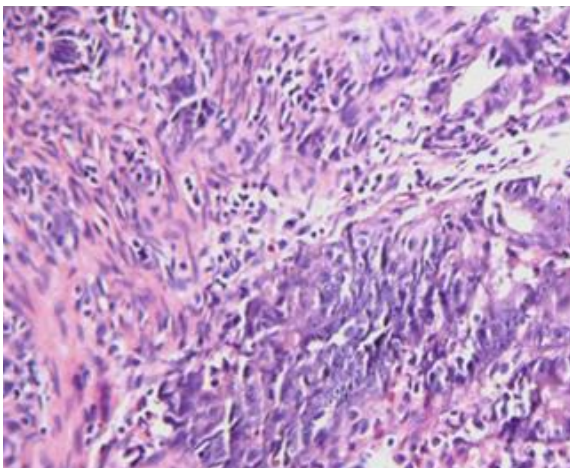


Figure 59. Low differentiated colorectal carcinoma. H&E staining, x20.

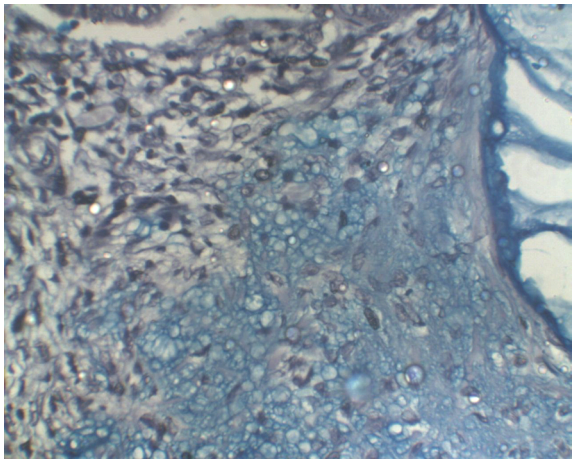


Figure 60. Low differentiated colorectal carcinoma. Blue Alcian staining, x40.

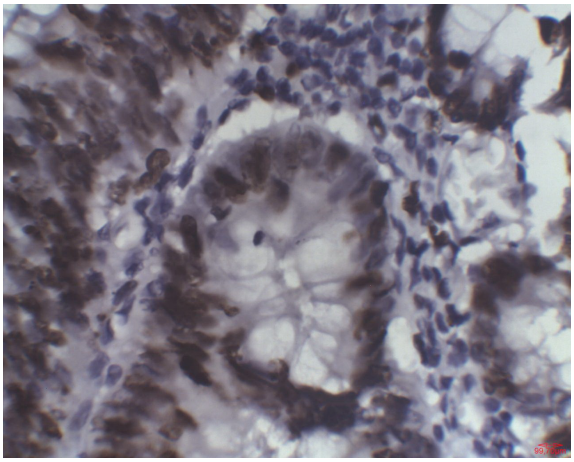


Figure 61. Strong nuclear reaction of Ki-67 on sections of colorectal cancer (+++). X6

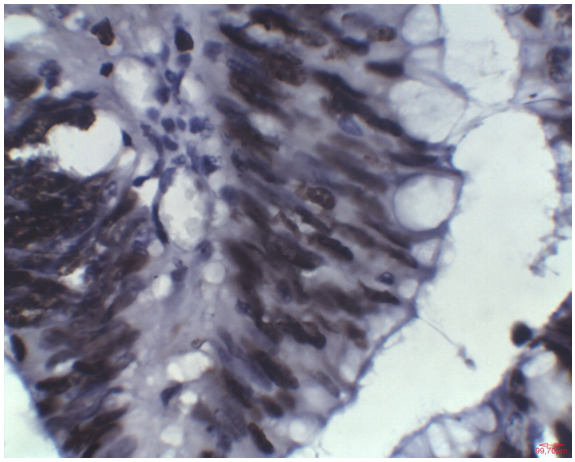


Figure 62. Nuclear Reaction of Ki-67 in the Cellsof a colorectal cancer. Ob. X60**.**

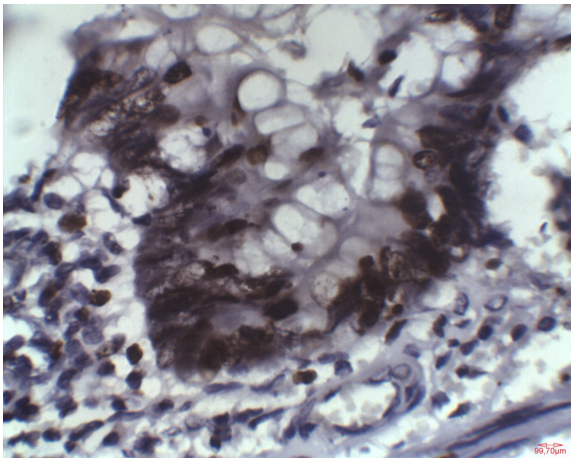


Figure 63. Intense nuclear (+++) reaction of Ki-67on sections of colorectal cancer.

In cases with a strong positive response to Ki-67 (+++), prognosis is worse, with invasion of the perirectal tissues, regional lymph nodes and metastases. In these situations there is a direct correlation between the expression and accumulation of the Ki-67 protein and the local, regional or distant extension.

We have not noticed any correlation between the intensity of the reaction and the age and gender of the patient or the exact location of the primitive tumor.

2.2.4. Discussions

Ki-67, marker of cell proliferation is associated with a low prognosis in colorectal cancer patients. Its expression is increased in patients with Dukes C or D colorectal cancer versus those in stage A or B. The Ki-67 along with other clinical-pathologic markers could be useful in the prognosis of patients with colorectal cancer.

The growth rate of cancer cells depends on their proliferative activity and cell death rate. Researchers evaluated the expressions of Ki-67, PCNA, MCM in 55 patients diagnosed with colorectal carcinomas and showed that the expressions of the three antibodies are directly correlated with the presence of metastatic lymph nodes but are independent of the age and location of the tumor. It can be concluded that their positive expressions in the mass of the main tumor are directly proportional to pathological stage and histological differentiation gradient (Katarzyna et al., 2008).

Neoplastic growth is characterized by uncontrolled proliferation well above the cell death rate, as well as loss of cell differentiation. For this reason a neoplasm means a cell growth disorder evidenced by excessive cellular proliferation. Determination of this proliferation can be used in the positive diagnosis and prognosis of neoplastic lesions, and from this point of view, Ki67 is a valuable tool. Exaggerated expression of this marker may suggest a disruption in the regularity of cell division, resulting in the appearance of an intensely-growing tumour.

The Ki67 marker is also used to determine the degree of aggressiveness and the metastatic potential of the tumour.

The Ki-67 monoclonal antibody recognizes an antigen located in cell nuclei in all cell cycle phases except G_0. The Ki-67 staining method is simple and can be used as a technique to estimate the proliferative activity, as a prognostic marker as well as a screening test in individuals with high risk (Mullerat et al., 2003; Oshima et al., 2005).

The value of this protein's expression has a normal limit in the free mucosa, being somewhat higher in adenomas, and the maxima in adenocarcinomas (Saleh et al., 1999).

Researchers found a correlation between the histological degree of malignancy and the depth of tumor infiltration in the wall (Dziegiel et al., 2003). Determination of Ki-67 may subdivide a group of patients with similar clinical symptoms into diagnostic and prognostic subgroups.

There were described several methods for identifying tumor vessels based on the ability of endothelial cells of vascular tissue to release antigens which can serve as markers on tissue included in paraffin, CD34 considered to be the best marker for neovascularization (De la Taille, 2000).

Modern management of colorectal cancer is multidisciplinary, with a major focus on preoperative assessment. This has become possible with the advancement of both medical imaging and immunohistochemical techniques. The formulation of a certain diagnosis and therapeutic protocol is a common element for aspiring multidisciplinary effort made by surgeons, oncologists and pathologists. In order to achieve preoperative staging of rectal cancer, it should be known local extension of the tumor and systemic dissemination of cancer cells. Formulation of a therapeutic protocol and prognosis of colorectal cancer depend on tumor stage, tumor type, invasion of lymph nodes, as well as whether or not the sphincter apparatus and neighborhood fascia are involved.

Neoangiogenesis occurs independently of malignant transformation, involves growth factors, extracellular matrix enzymes, endothelial cell migration and proliferation, lumen formation and anastomosis with other vessels, in relation to phenotypic and tumor genetic changes. Some authors have experimentally demonstrated that neoplastic cell populations release angiogenic molecules "in vivo", before their neoplastic transformation reaches the

level of formation of a solid tumor. Tumor growth and transformation of tumor cells into an angiogenic phenotype are associated with increased secretion of angiogenic molecules, such as fibroblast growth factor, FGF and endothelial proliferation factor VEGF. In addition, it has been shown that a tumor develops a pronounced angiogenic phenotype when angiogenesis inhibitors (anti-angiogenic factors) are suppressed during tumorigenesis, such as the case of thrombospondin, which normally helps keep the vessels in a non-angiogenic status (Park et al., 2014).

Initially, was used antibody measurement for CD31, CD34 markers and for growth factor VIII, but was recently used the quantification of CD105 endothelial cell marker expression (Ottaviano, 2015; Goldis, 2015). It seems, however, that this marker is not specific only to vascular endothelium (Agaki, 2001).

Neovascularization that crosses the tumor mass develops rapidly and presents itself as a disorganized chaotic network with tortuous, thin walls; as a result, the irrigation of different tumor segments is differentiated, with deficiencies in some segments which can lead to tissue necrosis. In this context it was found that the tumor aggressiveness is much higher in the periphery than in the tumor center, in terms of microvascular density per mm2 (Romani, 2006).

Structural features of the vascular network in tumors are: flattened endothelium, no differentiation between arteries and veins, poor structural stability, lack of parietal contractile elements, lack of receptors, incomplete formation of basal membrane, lack of lymphatic formation (Corines et al., 2018).

Most of the studies (Brouwer et al., 2018) show a connection between tumoral angiogenesis and metastasies but, there are differences caused by the method used for immunological staining of vessels; vimentine has a lower specificity then VIIIth factor and this then CD34. Also there are significant differences between the degrees of differenciation, low, intermediary and high.

P53, also known as "genome guardian" is one of the most affected tumor suppressor gene in the case of colorectal neoplasms. Mutations in this gene, appeared in the process of carcinogenesis, located on chromosome 17 occurs in more than 50% of carcinomas during the process of tumorigenesis. These mutations are linked with altered DNA replication and progression to cancer. The involve of this gene in the occurrence of recurrences and prognostics of colrectal cancer is questionable (Kahlenberg, 2003).

Some studies on groups of patients make from p53 gene and its mutation a marker of relapse and life expectancy (Kahlenberg, 2000), while other studies have not found the existence of such a role for the gene. Regarding the ordinary response to radio and chemotherapy p53 mutation showed a high degree of resistance to them. This mutation does not respond to 5-fluoro-uracil and methotrexate.

Molecular biology studies carried out on parts of resection of colorectal carcinoma correlate p53 gene mutations with polyp-carcinoma sequence. This neoplastic process begins with the activation of oncogenes (Ki-RAS), inactivation of tumor suppressor genes (p53 and Ki-RAS DCC), followed by suppressor gene mutations during progression from adenoma to carcinoma. These mutations type "missense" is performed simultaneously with the loss of wild-type allele, with a prolonged half-life, which makes these changes to be detectable immunohistochemically (Levine, 1991). Cases in which over 45% of proximal colon cancers

develop "de novo", ignoring the polyp-carcinoma sequence are due to genomic instability associated with a defect in mismatch repair of DNA.

Since 1988, it has been shown that the immunohistochemical determination of Ki-67 may have clinical application in the selection of patients with colorectal cancer who may benefit from radiotherapy and/or chemotherapy, particularly those with unresectable or locally recurrent tumors (Shepherd et al., 1988).

Research on colorectal carcinomas using immunohistochemical techniques with Ki-67 protein is simple and relatively easy to apply. The results are reproducible using the MIB 1 antibody with which excellent stains can be obtained, even on the classically fixed paraffin blocks 1 (Uzmaet al., 2008). *Ki-67 expression is high in non-mucosal adenocarcinomas, highly or moderate differentiated, and is low in those that are low differentiated with mucin secretion. This last type of tumour corresponds to an advanced Dukes stage. Thus, there is a close association between the histological grade, type and stage of the tumour.*

2.2.5. Conclusions

Increased expression of the Ki-67 marker is generally associated with a low prognosis of survival, especially in undifferentiated or low differentiated cases of colorectal carcinomas. The Ki-67 along with other clinical-pathologic markers could be useful in the prognosis of patients with colorectal cancer.

2.3. SURGICAL AND ENZYMATIC TREATMENT IN CHRONIC PANCREATITIS

2.3.1. Introduction

Generally, the treatment of chronic pancreatitis consists of conservative and surgical treatment. The current development of interventional endoscopy techniques links the two above-mentioned treatments, offering less invasive solutions.

In the treatment of chronic pancreatitis, a progressive approach is needed. Establishing any type of treatment is useless if the patient does not follow the recommendation to completely abstain from alcohol and/or drugs.

The pancreas synthesizes and secretes more than ten enzymes that hydrolyze carbohydrates, fats and proteins, especially in the lumen of the small intestine. In the evolution of chronic pancreatitis, secretory capacity of the pancreas and, implicitly, intraluminal digestion decrease. In chronic pancreatitis of alcoholic etiology, malabsorption usually does not occur earlier than ten years from the beginning of clinical symptomatology (Dimango et al., 1973). As a result of the normal back up of pancreas secretory capacity, the inflammatory process must destroy more than 90-95% of the secretory parenchyma before malabsorption occurs.

To reduce malabsorption in exocrine pancreatic insufficiency, it is necessary to have a sufficient enzymatic level in the duodenal lumen at the same time with food penetration. Malabsorption occurs if this level is below 5-10% of the maximum normal enzyme flow rate. As a consequence, sialorrhoea can be prevented if during the digestion

period the average level of lipase present in the duodenum chyme reaches 40-60 U / ml. This means a required lipase intake of 35,000 - 40,000 U at each meal.

However, administering adequate amounts of lipase that reach undegradated in the duodenum encounters a number of difficulties. The ingestion of unprotected enzyme drugs is followed by the almost complete destruction of lipases by the gastric acid medium while the proteases pass through the stomach significantly better.

In addition to acid stomach denaturation, lipases from enzyme drugs are inactivated by proteolytic destruction in the intestinal lumen of patients with chronic pancreatitis, as well as an endogen lipase in healthy individuals. Only small amounts of active lipase are reaching into the duodenum and this requires administering an amount of five to ten times greater than that is intraduodenally necessary.

Pancreatic stimulation of digestion are hormone-controlled and mediated processes (Berry, 2014).

Pancreatic insufficiency requires the initiation of substitution enzyme therapy as an etiological therapy for cystic fibrosis, pancreatic cancer, acute and chronic pancreatitis.

The first step in determining the effectiveness of using of pancreatic enzyme therapy is to determine whether malabsorption syndrome is due in most part to pancreatic exocrine insufficiency (Dominguez-Munoz, 2011).

The large number of drugs that the patient has to swallow makes it difficult to treat in the long time. On the other hand, capsules protected against gastric digestion are not superior to those unprotected because they remain in the stomach throughout the digestion period and are eliminated in the duodenum only late when digestion is complete. The efficacy of pancreatic enzyme preparations can be enhanced by gastric acid inhibitors: H2 blockers and Na-K pump blockers (Dominguez-Munoz and Iglesias-Garcia, 2010). Another possibility is given by the appearance of enteric-protected pancreatin microspheres.

The purpose of this study is to assess the usefulness of qualitative and quantitative analyses of pancreatic chronic focal diseases under enzymatic treatment.

2.3.2. Materials and methods

Our study group consists of 612 patients with pancreatic disease. They were admitted to the Fourth Surgery Unit, Iasi, between 2010-2018. Of these, 290 patients (47.39%) had tumoral conditions (benign or malignant) and 322 patients (52.61%) of inflammatory conditions.

Of the total patients diagnosed with pancreatitis, 61 patients were hospitalized and operated for chronic forms (23.7% of total pancreatitis) and these represent the study group. 51 patients were male and the avarage age was 41.6 years. The predominant symptom is pain, present in 90.1% of cases, followed by weight loss (85.2%), steatore (21.3%), obstructive jaundice (16.4%) and digestive haemorrhage (5%).

From the studied group, 81.9% of patients were operated in the first five years from the onset of the disease, 14.7% between 5 and 10 years, and 3.2% after 10 years of evolution. The average development period was three years and nine months.

2.3.3. Results

Suppression of pain can be achieved by several conservative measures, for the vast majority of patients. Surgery is only necessary in cases where the pain is associated with the existence of an inflammatory tumour of the head of the pancreas or with a major complication of the disease. The measures necessary for the conservative treatment of pain are diet, analgesics, therapeutic inhibition of pancreatic secretion and endoscopic maneuvers.

Regarding the treatment of chronic pancreatitis, following our professional experience and research results of this group of patients, we propose a protocol for their management (**Figure 64**).

The results obtained from this study showed that in most cases the substitution treatment of pancreatic function in patients diagnosed with chronic pancreatitis is efficient. Combating steathoreea and implicitly reducing the pancreatic enzyme requirement in the intestine significantly reduces painful symptoms, but also inflammatory and autophagic phenomena in the gland (**Figures 65, 66, 67**).

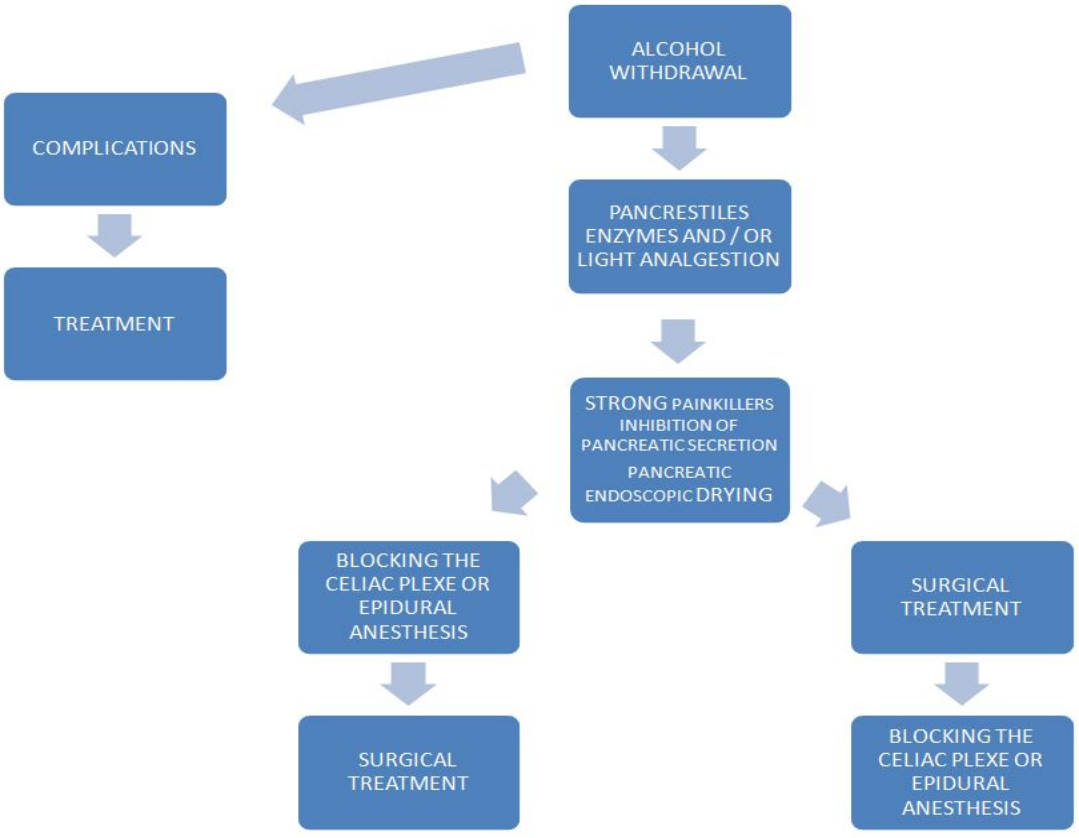


Figure 64. Management protocol of patients with chronic pancreatitis

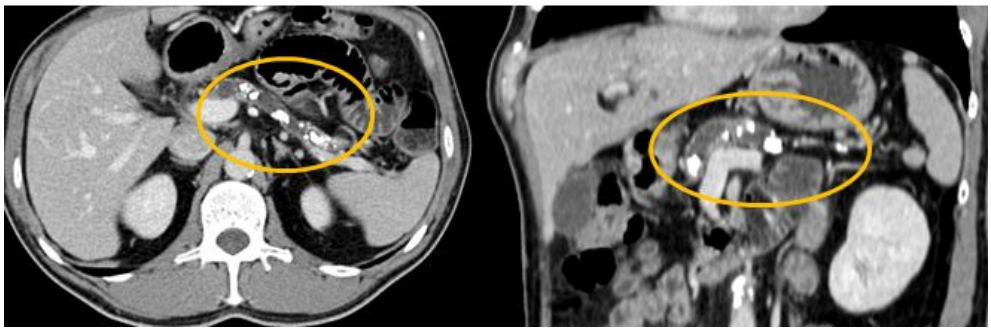


Figure 65. CT - Atrophic pancreas with ductal dilatation and intra and periductal calcifications

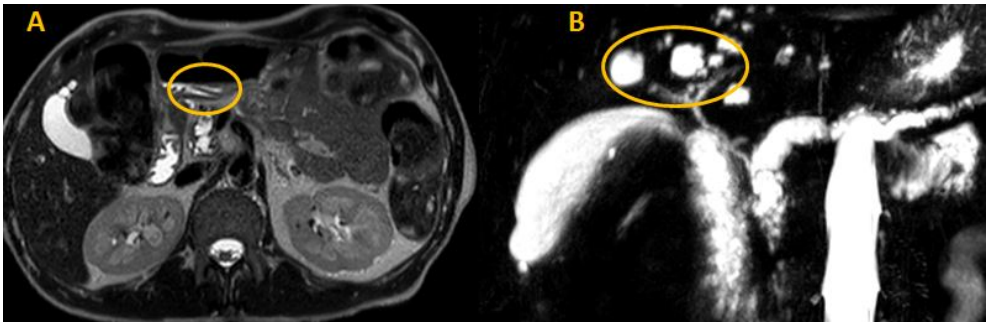


Figure 66. MRI - moniliform dilatation Wirsung duct, intraductal signal, atrophic pancreas

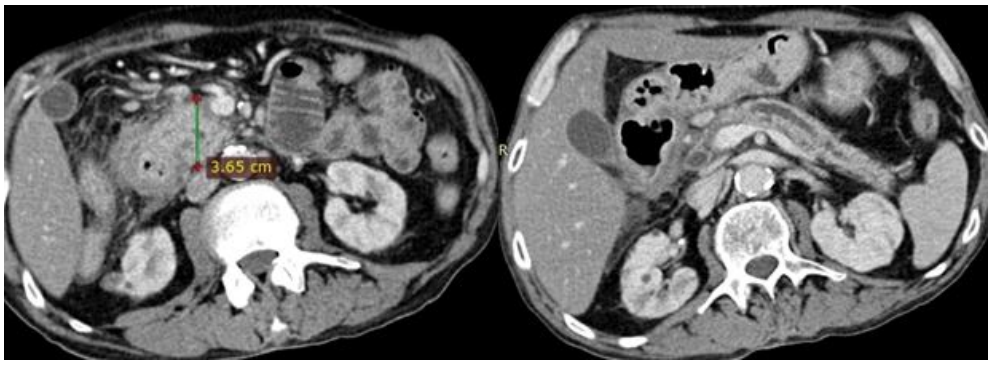


Figure 67. Increased volume of cephalic pancreas, inhomogeneous, infiltrated aspect of peripancreatic fat, thickening of the duodenal wall; normal corporeal and caudal pancreas; Wirsung duct dilated all the length

In this regard, we propose a scheme for the application of drug treatment, customizable and adaptable according to the patients' response to the different types of pancreatic substitution medication (**Figure 68**).

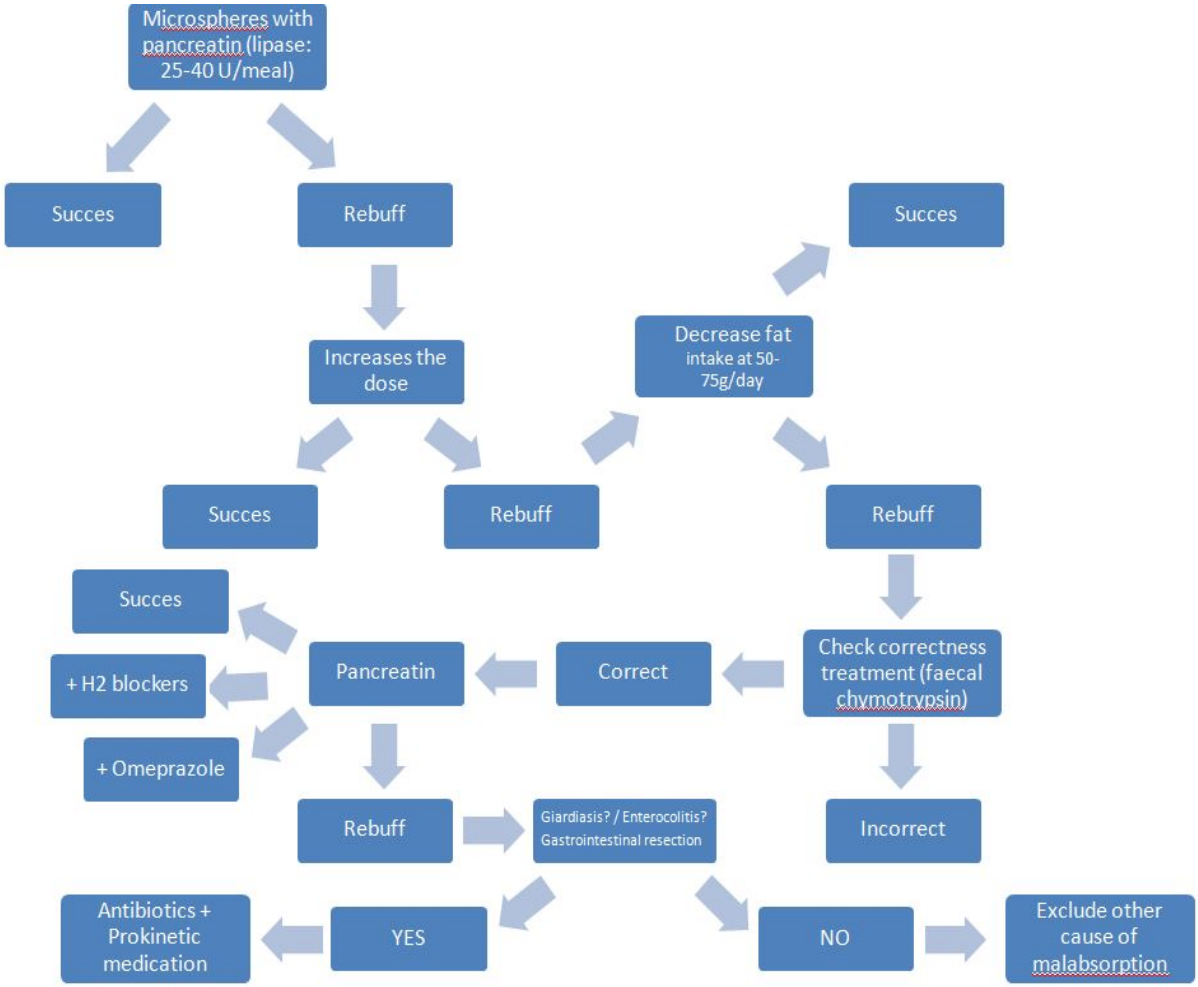


Figure 68. Adaptable scheme of medical treatment in chronic pancreatitis

In our study, we considered stabilized a patient without pain or with sporadic pain of low intensity, whose generall condition is good, which has increased in weight with an unchanged carbohydrate balance, over a period of at least five years.

Even under these circumstances parenchymal lesions and/or chronic pancreatic duct can cause exocrine and endocrine deficiencies.

We considered as a failure a patient with further pains of the same intensity or higher compared to the period before the intervention and with a marked deterioration of the general condition. This result is mainly due to non-compliance with diet and alcohol abstinence (**Figures 69 and 70**).

2.3.4. Discussions

For most patients with exocrine pancreatic insufficiency, enteric-protected microspheres (eg Creon) administered at the beginning of the meals are considered elective treatment.

On the contrary, patients with gastric resections or gastroenteroanastomoses with an accelerated gastric emptying, require administration of pancreatin granules or powder preparations. Patients with aclorhidhy, including those treated with IL-blockers or Na-K

pump inhibitors, may be treated with conventional gastric unprotected pancreatin preparations.

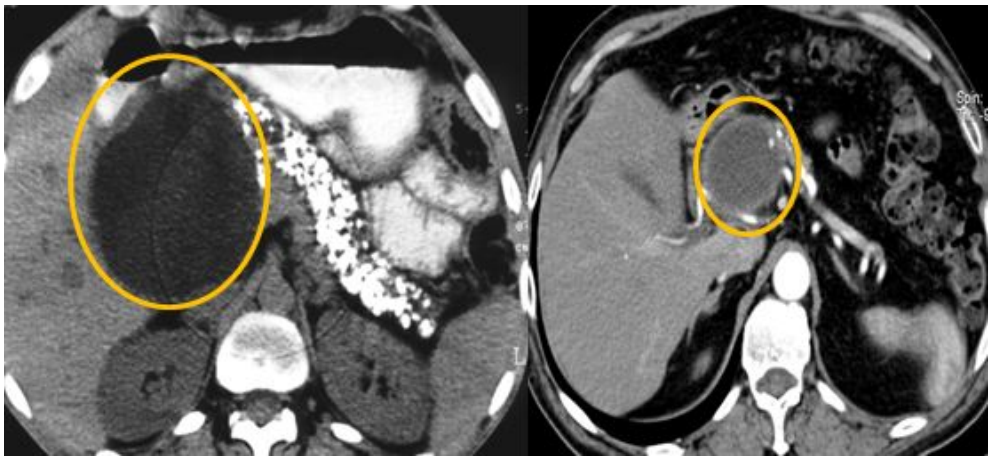


Figure 69. Cephalic pancreas with lipomatous degenerated parenchyma, secondary ducts and microchists; normal corporeal and caudal pancreas; dilatation of the main pancreatic duct

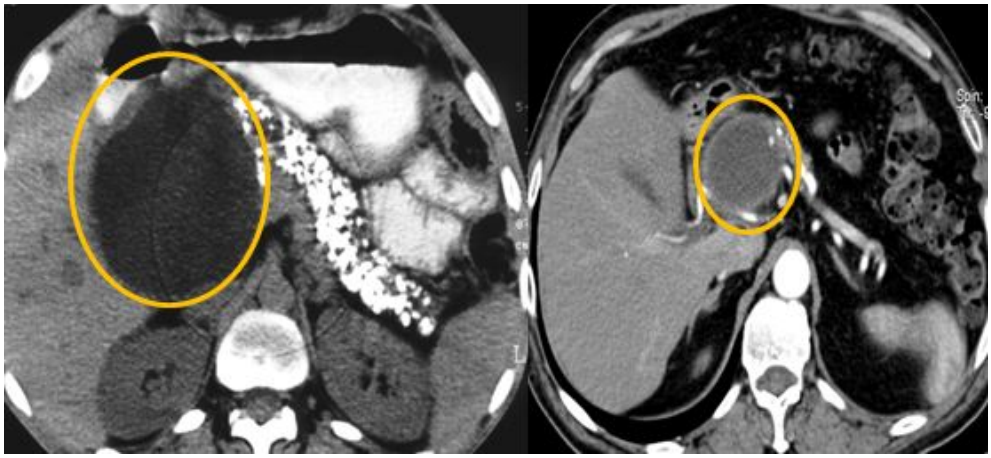


Figure 70. Cephalopancreatic pseudochist

Furthermore, some authors attempted to block celiac plexus or epidural anesthesia as the last conservative option before indicating surgical treatment.

Chronic pancreatitis, with its intractable abdominal pain and adjacent organ damage, remains a difficult condition to manage despite considerable advances in endoscopic techniques and a number of randomized surgical intervention trials. Wide variations in the etiology and presentation of the disease makes it difficult to compare the true potential of many currently used techniques and most options still exhibit significant failure and complication rates. Although a number of randomized trials comparing different sur- gical approaches have been reported, there still is a clear need for further study to understand which procedures are optimal for any given CP etiologies. The decision as to which procedure is indicated for each patient should be guided by the clinical setting, the individual's unique anatomic and pathological findings, and indi- vidual surgeon and institutional experience (Tillou et al., 2017).

Chronic pancreatitis is first asymptomatic but in an advanced stage it is characterised by abdominal pains. The causes of pain in CP may result from an increased pressure in the pancreatic duct, damaged pancreatic nerves, pancreatic ischaemia, local complications of CP, such as narrowed duodenum, large pancreatic pseudocysts and biliary obstruction. In order to control pain in chronic pancreatitis abinding general recommendations such as diet and smoking cessation is needed. If it does not achieve expected effect the next step would be a substitutive enzymatic therapy, administration of antioxidants and analgesics. Paracetamol (N-acetyl-paminophenol) is one of the analgesics recommended for the treatment of mild or moderate pain in chronic pancreatitis (Olesen et al.,2013; Siepsiak et al., 2016).

It is very important to administer a sufficient dose of lipase; those of amylase and protease are less necessary in most patients. To decreasse a major steatorrhea to an acceptable level, a dose of at least 25,000 - 40,000 U lipase / lunch (at 4-5 meals / day) is required. In most cases, these doses need to be doubled. The effectiveness of treatment should be controlled primarily from the clinical point of view (body weight, stool consistency).

If the treatment response is unsatisfactory even at high doses of enzymes, patients need to change their diets in the sense of fragmenting them (5-6 small lunches / day) and reducing the amount of daily fat ingested to 50-70g. If and with these measures the patient's clinical condition does not improve, patient's compliance with the therapeutic indications should be checked. This can be done indirectly by dosing of the fecal chymotrypsin, which should be at a normal level in a patient who respects prescribed doses. If its value is low, an insufficient intake of additional enzymes should be suspected.

In these patients, the combination of proton blockers or omeprazole may be attempted, particularly in children with cystic fibrosis. Replacing fat from food with medium chain triglycerides can improve lipid absorption, but many patients complain about their unpleasant taste. Sometimes, especially in patients with gastrointestinal resections and intestinal infections with Giardia Lambi or bacteria, they can contribute to the malabsorption syndrome.

At present, the question arises whether existing enzyme preparations have a role not only in suppressing malabsorption but also in suppressing pain in patients suffering from chronic pancreatitis. Existing data suggest that in severe pancreatitis most patients do not respond to medical treatment. It is assumed that in the near future a whole range of stable drugs with lipase will appear in the treatment of pancreatitis. However, their practical benefit will require a reserved appreciation (Duggan et al., 2010, Anderson et al., 2016).

Anti-inflammatory enzymes favor pancreatic dissolution and excretion, decrease the degree of pancreatic fibrosis and accelerate drug diffusion to the lesion. Currently, new formulations of anti-inflammatory enzymes are successfully prepared to improve their functional characteristics, pharmacokinetic properties and anti-inflammatory efficacy. They aim at increasing enzymatic stability and provide different routes of administration that improve their effectiveness and reduce their side effects and toxicity (Yang et al., 2018).

Medical treatment should ideally mimic the physiological intestinal status that is characterized by major digestion in the proximal intestine and the rapid decrease in lipolytic activity as intestinal chyme advances into the digestive tract. Because enzyme

replacement therapy is usually life-long, it is necessary to carefully study the potential side effects of these high-dose enzymes.

2.3.5. Conclusions

Pancreatic insufficiency due to chronic pancreatitis is not a simple enzymatic deficiency, but an interactive complex of secretory, motor and endocrine functional disorders. Therefore, developing drug therapy will require not only the simple administration of enzymes in the intestine but also the restoration of the integrity of disruptive digestive functions.

2.4. UNDERSTANDING THE CHRONIC PANCREATITIS INJURIES BY USING AN EXPERIMENTAL MODEL

2.4.1. Introduction

The concept of chronic pancreatitis has been stated in our country much later than acute pancreatitis. Gastroenterologists and, in particular, surgeons discuss less about this disease, which exists and will likely exist as long as alcohol consumption is maintained at a high level.

The individualisation of chronic pancreatic condition was first observed by anatomopathologists and surgeons, and more late it was achieved the clinical and morphopathological integration of the disease.

Chronic pancreatitis is defined by morphological criteria (inflammatory disease characterized by irreversibility of morphological lesions), clinical (presence of pancreatic pain syndrome) and functional (progressive deterioration of functional ability of the organ) (Hue et al., 2006).

This manuscript proposes a synthesis of the etiopathogenic, diagnostic and therapeutic data in chronic pancreatitis based on actual information correlated with the results of our experimental study.

Pancreatitis classification of Marseilles in 1988 gives a relatively current view of the inflammatory pathology of the pancreas (Singer et al., 1984). Thus, pancreatitis is divided into acute pancreatitis that is not defined as a disease but only as a group of lesions that can affect the pancreas or peripancreatic tissues. These include edema, adipose necrosis or haemorrhagic necrosis. These injuries are generally reversible except in rare cases, where necrosis is followed by a stenosis of pancreatic canals that will cause obstructive chronic pancreatitis above the obstruction. Pancreatic haemorrhagic necrosis is mostly peripancreatic, can increase in volume and be the origin of necrotic pseudocysts limited by fibrosis to neighboring organs. Infection of pseudocystis gives rise to abscesses. Pseudocysts are the most common cause of rare stenosis of pancreatic canal.

Acute pancreatitis are of various extrapancreatic causes, such as: biliary lithiasis, surgical or abdominal trauma, medications, papillary endoscopic catheterization.

Intrapancreatic causes include: pancreatic cancer and especially chronic pancreatitis that complicates at the beginning with acinar necrosis.

Chronic pancreatitis is characterized by fibrosis, loss of exocrine parenchyma, then endocrine and canalicular lesions.

Research into the pathogenesis and treatment of pancreatitis faces many obstacles due to the difficult anatomical approach of this organ and also due to a difficult clinical prognosis. Most current knowledge about pancreatitis is based on research on experimental animals models (Jin and Sik, 2014).

Experimental models of chronic pancreatitis aim to reproduce morphopathological changes: cell loss, chronic inflammatory infiltration, formation of intraductal protein obstructions, calcification and fibrosis. Despite the effort to clarify the pathogenesis and natural evolution of chronic pancreatitis, a relevant and satisfactory experimental model has not yet been established (Aghdassi et al., 2011).

2.4.2. Material and methods

Our study was conducted in the experimental laboratory of the 3rd Surgery Clinic, in Iasi, within the concerns about the etiopathogenesis and treatment of chronic pancreatitis. It have been developed an experimental model to produce this disease in dogs.

The experiment was performed on 18 dogs, in which the intraduodenal ligation of the pancreatic duct apertures was performed in two cases and the obstruction of the pancreatic ducts by intraparenchymatous, intraoperative neoprene injections in the other 16 cases.

The experimental study respects the principles of the Helsinki Declaration on Animal Rights.

2.4.3. Results

We investigated the lesions through intraoperative pancreatic tissue collected at 2- 3 week intervals, 3-6 months and at necropsy.

Monitoring of glycemia was done weekly by observing and noting its variations. It was demonstrated the integrity of the Langerhans islands, with moderate decrease of their volume.

At the time when acinar tissue sclerosis was obtained, six months after neoprene injection, pancreas with chronic lesions was transplantated to a pancreatectomized animal. The pancreas was heterotopically fixed in the right iliac fossa at the spleen vessels.

It have been observed aspects regarding the pathogenesis, clinical, evolution and treatment of chronic pancreatitis compared to acute pancreatitis.

2.4.4. Discussions

Experimentally induced pancreatitis in rats using cerulein is the most commonly used experimental animal model of acute pancreatitis. The benefits of this model are

reproducibility and the fact that it is economical (Lampel and Kern, 1977;Saluja et al., 1985) .

The acute pancreatitis model induced with bile salts was accepted as a representative model for severe acute pancreatitis with pancreatic necrosis (Aho et al., 1980, 1983). The experiment is performed by injecting the substance through the canalicular opening and infusing 0.2 to 0.3 ml of 3% to 5% sodium taurocholate in a retrograde way. Among the difficulties in achieving this model are the abdominal incision and the experience required to introduce the cannula through the opening of the pancreatic duct. This experimental model induces severe hemorrhagic necrosis of the pancreas in a relatively short period with the appearance of non-uniform pancreatic lesions.

Another model of experimental induction of acute pancreatitis is that of choline-deficient diet supplemented with ethion. The induction of acute hemorrhagic pancreatitis occurs in about 5-10 days. The main disadvantage of this model is given by the occurrence of acute pancreatitis that appear only in young female mice (Lombardi et al., 1975).

Acute necrotizing pancreatitis model induced by L-arginine is achieved by a single intraperitoneal injection with an excessive dose (Tani et al., 1990).

Changes observed in the pancreas after ligation of the pancreatic duct vary with the animals used and simulate that the ampulle is obstructed by a bile stone. Bile salts replenish in the pancreatic duct and induce acute pancreatitis. Since the pressure in the pancreatic duct is greater than in the bile duct, it is known that pancreatic juice refills in the bile ducts only in the presence of obstruction with a large orifice and not vice versa. Pancreatic inflammatory response rarely occurs in patients with Vater ampoule cancer, even after the pancreatic duct has been obstructed by the tumor, which makes the validity of this hypothesis questionable (Steer, 1993; Lerch et al., 2013).

If the pancreatic duct is ligated in rats, initial morphopathological manifestations such as pancreatic edema, infiltration of inflammatory cells, hyperamylase are compatible with acute pancreatitis, which lead to chronic pancreatitis over time. Thus, injuries such as atrophy in acinar cells and fibrosis will occur (Oshio et al., 1991; Yamamoto et al., 2006).

Of the various experimental models of chronic pancreatitis, the most commonly used are surgical ligation of the pancreatic duct (obstructive), ethanol intake, repeat injection of cerulein, and toxic-induced models.

The obstructive model is based on the ligation of the pancreatic duct and induces glandular fibrosis. Clinical and pathological manifestations after canal ligation are dependent on the species and type of animal used.

Thus, in rats the ligation results in cellular atrophy and fibrosis, without a marked inflammatory reaction, and in mice induces a uniform fibrosis. In these situations, duct hypertension suggests that pancreatic duct hypertension contributes to the initiation and development of chronic pancreatitis (Yamamoto et al., 2006).

The model realised by repeated administration of cerulein induces recurrent acute pancreatitis episodes leading to chronic lesions (Neuschwander-Tetri et al., 2000).

Experimentally, alcohol intake did not cause chronic pancreatitis despite the long duration of the experiments. On the other hand, the combination of alcohol and other toxic agents, such as cerulein or lipopolysaccharide, leads to the occurrence of pancreatic fibrosis (Vonlaufen et al., 2007).

Toxic induced pancreatitis by administration of dibuthyddine dichloride is used to induce chronic pancreatic lesions of the edematous type (Sparmann et al., 1997).

The use of L-arginine in the induction of chronic pancreatitis leads to the appearance of a severe necrotic form, causing progressive degeneration of the pancreas. Even though this experimental model is simple to perform and has features similar to human lesions, their histological appearance differs by progressive replacement of adipose tissue (Weaver et al., 1994).

Time obsevation of animals with endocrine pancreas transplanted has been demonstrated the effectiveness of complete destruction of external neoprene secretion, at the same time preserving internal function, Langerhans Islands remaining functional. Unlike dogs, in rodents, pancreatic exocrine function shows a significant decrease 2 weeks after duct ligation. The method of maintaining the pancreas with intense lesions of chronic pancreatitis without secretory activity by blocking with inactive substances such as latex or neoprene can still be an alternative.

Pancreas transplantation with chronic pancreatitis experimentally induced in the iliac vessels of the beneficiary produces an important surgery trauma, in cases where either a triple Salambier derivation or a resectional cephalic process is used, on a pancreas that also exhibits body-caudal lesions.

Most experimental studies on dogs are those based on pancreatic and/or alcoholic toxic diets. Induction of a chronic pancreatic reaction by obliteration of neoprene pancreatic ducts produces morphopathological manifestations close to human ones at a low cost in a relatively short period of time but does not affect endocrine function as well.

2.4.5. Conclusions

Each experimental model has its own advantages or disadvantages. In spite of research in the field, there are still many questions to be solved. The results encourage us to continue the research and to choose genetically modified animals because are closer to the human one.

2.5. Mathematical models of cancer angiogenesis

Nowadays, conventional cancer therapies are the surgical and oncologic treatment. Theoretically, surgical oncology could totally removed the tumor cells (zero-order kinetics). By oncologic adjuvant therapy only a fraction of tumor cells are killed (first-order kinetics) (Pollock, 2008; Feig, 2006; Connell, Hellman, 2009; Gazda Lawrence, 2001).

Chemotherapy and radiotherapy have significant side effects such as anemia, alopecia, nausea and vomiting, nerve problems, skin problems and these treatments

are toxic to all cells (Page, Takimoto, 2001; Perry, 2008, Samson et al., 2012).

Recent progress in manipulating atomic and condensed matter systems has instigated a surge of interest in nonequilibrium physics, including many-body dynamics of trapped ultracold atoms and ions, near-field radiative heat transfer, and quantum friction (Kovács et al., 2014).

Under most circumstances the complexity of such nonequilibrium systems requires a number of approximations to make theoretical descriptions tractable. In particular, it is often assumed that spatially separated components of a system thermalize with their immediate surroundings, although the global state of the system is out of equilibrium.

This powerful assumption reduces the complexity of nonequilibrium systems to the local application of well-founded equilibrium concepts. While this technique appears to be consistent for the description of some phenomena, it fails for quantum friction by underestimating by approximately 80% the magnitude of the drag force (Intravaia et al., 2016).

By angiogenesis new blood vessels, which occurs normally are formed in the human body and this process is precisely controlled by specific factors. When tumor proliferation begins it developest stops, because the diffusion of oxygen through tissues is limited. It takes place only duering the initial "avascular phase" of tumour growth. Than, during the "vascular phase", its own blood vessels grow (Folkman J, 1971, 1972, 1995).

The avascular tumour growth has been widely studied theoretically through the C. D. Little et al. (eds.), Vascular Morphogenesis: In Vivo, In Vitro, In Mente © Birkhäuser 1996 206 Chaplain and Onne use of mathematical models (Chaplain, Orme, 1996; Li, 2016).

Tumours have to break through the strict control of angiogenic factors, a process called angiogenic switch (Bergers, Benjamin, 2003).

Accordingly, if the tumour can be kept in an avascular dormant state it will be unable to grow in size (Kerbel, 1997).

By using antiangiogenic therapy, tumour cells cannot develop resistance toward the antiangiogenic drugs and and these drugs are relatively nontoxic (Kerbel, 1997; Pulido, Itty, 2009).

Antiangiogenic therapy is our main goal as cutting edge minimal invasive solution (Pluda, 1997; Leszczynski et al., 2019).

The Riccati equation is used in the calculus of variations of homogeneous spaces (Ricatti, 1724).

A striking feature of the quantum mechanical interaction between atoms or molecules and the electromagnetic field is the existence of dispersion forces such as Casimir–Polder and van der Waals forces (Carvalho et al., 2018; Pinto, 2018).

In such a framework, the quantum paths in imaginary time (between 0 and = 1/ kT, where k is the Boltzmann's constant and T the absolute temperature) is equivalent, in classical terms, to polymer chains that form closed loops of length. These polymer chains are in a state of random walk and the pair correlation function for points along each of them can be evaluated (Hoye, Brevik, 1992).

In this context, in this study, similar results with those from are obtained by means of a Ricatti's procedure induced by possible correlations through the compatibility of the

thermal radiation-classical damped oscillator dynamics. Thus, an analyzis method for the dynamics of polymeric chains is generated (Feynmann, Hibbs, 1965; Paun et al., 2016).

As a result, the aim of our study is to quantify the antiangiogenic cancer therapy by Riccati's equation, in order to prevent tumour's growth.

2.5.1. Material and methods

Hydrogels based on polymers (high and medium molecular weight chitosan, poly(vinyl alcohol), glutar-aldehyde), cross-linked with sodium sulphate or sodium tripolyphosphate were prepared.

Origial method consists in chitosan medium molecular weight (C, weight average molar mass of 210,000 g.mol-1 and degree of acetylation of 25%), gelatin B (G) of bovine origin, Phospholipon-90G (phosphatidylcholine) were used. MLVs were obtained by the thin film hydration method and SUVs by sonication (Desbrieres, 2014).

In order to achieve a controlled release of calcein, complex systems were prepared. As a first stage, calcein was encapsulated in liposomes. The suspension of calcein loaded liposomes was then added to the polymer solution prior to the introduction of GA as covalent crosslinking agent.

Then the crosslinking process continued with the introduction of ionic crosslinker (Sodium TripolyPhosphate-TPP, or sodium sulphate-S) following the same method. The hydrogels composition was modified in order to optimize of their properties, in terms of mechanical stability and drug release. The hydrogels were loaded with calcein and the amount of released drug was monitorized, observing for large time intervals a decrease of released calcein.

2.5.2. Results

Let us consider the second order differential equation characterizing a classical damped harmonic oscillator E1 with obvious notation for first and second derivatives of the relevant coordinate q in relation to time t. In relation E1 M is the inertial mass, R is the damping coefficient and K is the elastic coefficient.

Rewritten in the form of E2, these equations induce a two-dimensional manifold of phase space type - p and q - in which p correspond to momentum type variable and q to position type variable. The second equation E2 corresponds to the momentum definition. The equations E2 do not represent a Hamiltonian system, since the associated matrix is not an involution.

The statement becomes clearer if we put our system in its matrix form of E3. As long as M, R, K have constant values, this matrix equation, written in an equivalent form evidences the position of the energy and thus of the Hamiltonian.

Indeed, from equation E3 we can obtain E4, which proves that the energy in its quadratic form (the right part of equation E4 is the variation rate of the physical action represented by the elementary area from the phase space. We would like to showcase here is the fact that the energy does not have to obey the conservation laws in order to act like a variation rate for the physical action (**Figure 71**).

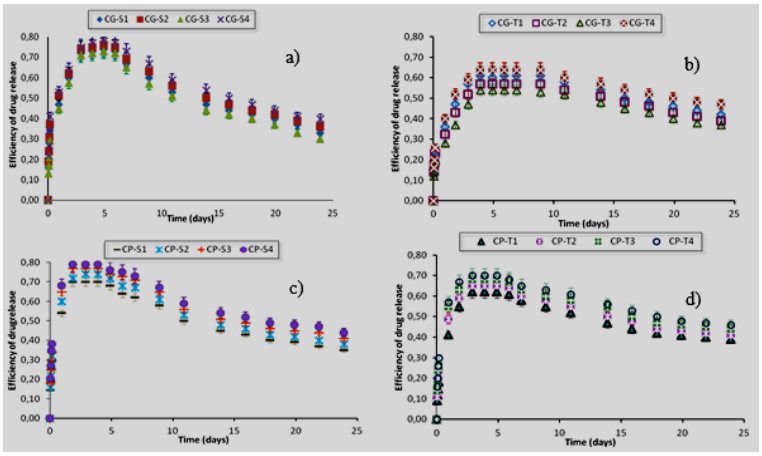


Figure 71. The release kinetics of calcein from hydrogels based on: chitosan and gelatin cross- linked with sodium sulphate (a) and sodium tripolyphosphate (b), chitosan and poly(vinyl alcohol) cross-linked with sodium sulphate (c) and sodium tripolyphosphate (d); graphic representation made after Desbrieres

We now ask what could be the conservation law, if it exists? To give an adequate answer we first observe that the equation E4 can be written as a Riccati type differential equation - E5.

Furthermore, let us note that the Riccati type equation E5 always represents a Hamiltonian system, describing the harmonic oscillator type dynamics - E6.

Relation E10 explicitly shows the relationship between the quanta and the statistical correlation of the two processes that represents thermal radiation. Moreover, it shows also the quanta value in the limit of the weak correlation, since we have E11, independent of any other consideration (**Figure 72**).

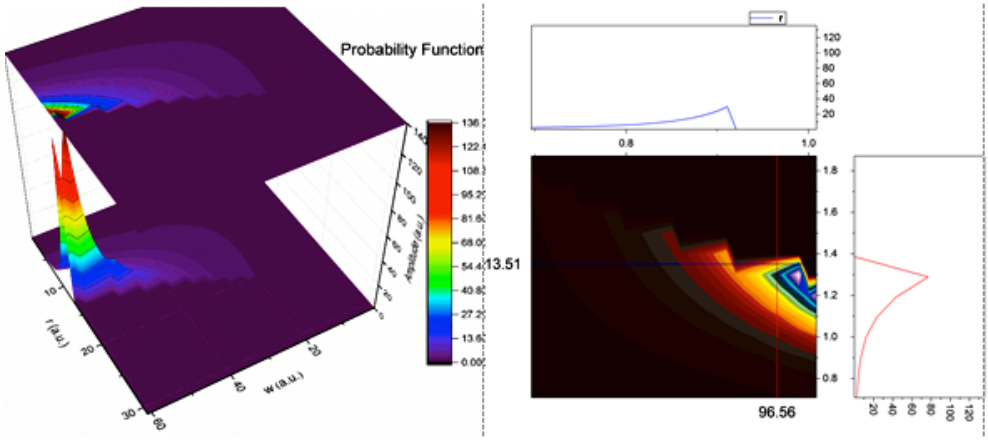


Figure 72. Quantization procedure through correlation of all statistical ensembles associated with local oscillators; 3D dependences (a) and contour curves (b)

But, in the general case, when the content in ε_o units of the thermal radiation field energy, as well as the correlation coefficient are arbitrary, it is important to note that the right

part of the equation E9 is actually the generating function of a special class of Pollaczek polynoms. More precisely, we can write E9 in the form of E12.

Their orthogonality relationship is given by E13 with the weighting function E14, where δ_{mn} is the Kronecker pseudotensor and Γ is the first order Euler function, generalization of the factorial function (**Tabel 18**).

Tabel 18. Equation algorithm

QEUATION NUMBER	EQUATION ALGORITHM
E1	$M\ddot{q}+2R\dot{q}+Kq=0$
E2	$\dot{p}=-\frac{2R}{M}p-\frac{K}{M}q \qquad \dot{q}=p$
E3	$\begin{pmatrix}\dot{p}\\ \dot{q}\end{pmatrix}=\begin{pmatrix}-2\frac{R}{M} & -\frac{K}{M}\\ 1 & 0\end{pmatrix}\begin{pmatrix}p\\ q\end{pmatrix}$
E4	$\frac{1}{2}M(p\dot{q}-q\dot{p})=\frac{1}{2}\left(Mp^2+2Rpq+Kq^2\right)$
E5	$\ddot{\phi}+\dot{\phi}^2+2\mu\dot{\phi}+\omega_0^2=0, \phi=\frac{p}{q}, \mu=\frac{R}{M}, \omega_0^2=\frac{K}{M}$
E6	$\begin{pmatrix}\dot{p}\\ \dot{q}\end{pmatrix}=\begin{pmatrix}-\frac{R}{M} & -\frac{K}{M}\\ 1 & \frac{R}{M}\end{pmatrix}\begin{pmatrix}p\\ q\end{pmatrix}$
E7	$\frac{1}{2}\left(Mp^2+2Rpq+Kq^2\right)\cdot\exp\left\{\frac{2R}{\sqrt{MK-R^2}}\arctan\left(\frac{Mp+Rq}{q\sqrt{MK-R^2}}\right)\right\}=const$
E8	$w^2=\frac{Mp^2}{Kq^2}, r^2=\frac{R}{M}$
E9	$e^{-\beta\varepsilon_0}=\frac{1}{1+2rw+w^2}\exp\left[\frac{2r}{\left(1-r^2\right)^{1/2}}\arctan\frac{w\left(1-r^2\right)^{1/2}}{1-rw}\right]$
E10	$e^{-\beta\varepsilon_0}=\frac{1}{2(1+r)}\exp\left[\frac{2r}{\left(1-r^2\right)^{1/2}}\arctan\sqrt{\frac{1+r}{1-r}}\right]$
E11	$\varepsilon_0=kT\ln 2$
E12	$e^{-\beta\varepsilon_0}=\sum_{n=0}^{\infty}P_n^l(r)w^n$
E13	$\int_{-1}^{l}P_n^a(r)P_m^a(r)\rho(r)dr=\frac{\pi}{2}\frac{n+1}{n+a+1}\delta_{nm}$
E14	$\rho(r)=\sin\theta\cdot e^{(2\theta-\pi)\tan\theta}\left\|\Gamma(1+i\tan\theta)\right\|^2,$ $r\equiv\cos\theta,\theta\in[0,\pi]$

2.5.3. Discussions

This evolution could not be explained by the classical theories of drug release, based on diffusion, due to the high number of interconnected variables involved, so that we have taken into consideration the development of a new theoretical model.

Let us remember that in 1961, Landauer discussed the limitation of the efficiency of a computer imposed by physical laws. In particular, he argued that, according to the second law of thermodynamics, the erasure of one bit of information requires a minimal heat generation kT ln 2, where T is here the temperature at which one erases.

Its arguments run as follows: since erasure is a logical function that does not have a single valued inverse it must be associated with physical irreversibility and, therefore, requires heat dissipation.

A bit has one degree of freedom and so the heat dissipation should be of kT order. Now, since before erasure a bit can be in any of the two possible states and after erasure it can only be in one state, this implies a change in information entropy of an amount -k ln 2. In such a context, the idea that the polymer chains can present a intrinsic pseudointelligence can

be substantiated.

Through such a procedure, the probability distribution (for example E14 for the polymer amplitudes of a free harmonic oscillator can be found. Moreover, new methodologies can be intuited, such as the fractal one in order to analyze the polymer chains dynamics.

This is a general characteristic describing the Riccati type equations and the Hamiltonian's dynamic. Equation E4 can be obtained also by building from equations E6 the differential 1 - form of the elementary area from the phase space for harmonic oscillator type dynamics. Regarding the equation E5, it can be integrated by specifying the fact that the energy does not conserve anymore, but we find that another, more complicated dynamics variable will be conserved E7.

It results that the energy is conserved in a classical meaning if R becomes null or if the movement in the phase space is characterized by the line passing though origin, having the slope defined by the ratio between R and M. Moreover, the statistical character of energy reveals.

Indeed, equation E7 can be written as E8, that explicitly shows that the potential energy, up to an arbitrary constant, depends in an effective manner on the ratio of kinetic and potential energy of the local oscillator. This energy can be correlated with an exponential factor (Boltzmann factor) that can play the role of partition function on a particular ensemble of harmonic oscillators of the same frequency (Planck's oscillators) in the form of E9.

The similarity of the equations E8 and E9 shows that the ratio of the two energies of the oscillators is in fact a statistical variable through which they are determined. In such conjecture, the left side of this equation represents a thermal ensemble of energy ε_o, with the average β. It is inconvenient that the right side also depends on εo. However, this dependence is realized through the ratio w, which allows us to affirm that a statistical interpretation depends on the content in εo units of the thermal radiation field energy (Figure 72).

If the energy density is of ε_o order, then w ≈1 and the right part of equation E9 depends only on the correlation coefficient r of the two thermal radiation processes (one at high temperature and other at low temperature.

If the energy density is of ε_o order, then w ≈1 and the right part of equation E9 depends only on the correlation coefficient r of the two thermal radiation processes (one at high temperature and other at low temperature E10 (Born, 1963; Planck, 1972).

Thus, this quanta and also frequency are directly proportional to color temperature. This fact was widely discussed by Louis de Broglie that identify the action with entropy, in order to unify the physics in the so-called thermodynamics.

If we agree to interpret the energy as the energy of a photon, then the relation E12 is the starting point of a modern quantum state related to the coherence properties of the radiation.

Through such a procedure, the probability distribution for the polymer amplitudes of a free harmonic oscillator can be found. Moreover, new methodologies can be intuited, such as the fractal one in order to analyze the polymer chains dynamics.

We have established optimal methods for obtaining different compounds (especially polymers), or stabilization and physico-chemical testing of high confidentiality.

Using a Ricatti's procedure, which implies possible correlations through the compatibility of the thermal radiation-classical damped oscillator dynamics, we have shown both, the potential energy of the damped oscillator and the distribution function of thermal radiation are defined by similar relations.

In such a framework, the damping coefficient is directly related to the correlation coefficient of the distribution of the radiation, while the ratio between the kinetic and potential energies of the damped oscillator is directly related to energy distribution rate of thermal radiation. If the correlation coefficient is null, a procedure of quantification was obtained.

Then, the quanta value (radiation frequency is directly proportional to the color temperature) and the erasure of one bit of information results. The theoretical model is validated by the similarity between the experimental curves (Figure 71) and the contour curves (Figure 72b).

The Kubelka-Munk effect (diffuse reflection) is considered in non-homogeneous optical media, with arbitrary absorption and dispersion coefficients depending on depth. The Riccati equation applies to regular disturbance theory and its explicit results are derived for diffuse reflection and transmission of a finite thickness layer. It is presented the first-order disturbance solution of an anatomical structure, or more, with exponentially distributed absorption coefficients and dispersion. The implications for quantitative and qualitative study of non-homogeneous optic media must be considered for the purpose of determining immunohistochemical markers (Mandelis and Grossman, 1992).

The dimensions and elasticity of the vascular wall is reduced along the length of the arteries and this phenomenon alters the waveforms of the blood flow rate. The artery is divided into short sections where the properties are considered to be constant (approximate solution) or there are exact solutions incorporating the effects mentioned.

Such a solution to the Ricatti impedance equation is obtained by a substitution process and is used to develop an exact expression for the flow rate of blood in the artery. Transmission line equations are then combined into a single integrative expression for the entire artery, and an exact solution is evaluated.

This is the solution for the geometric and elastic conicity and uses the pulsatility index. This explains precisely the effects of exponential convex, and this formula can be used to improve existing study on arterial models that use the less accurate and less difficult computational solution (Myers, 2004; Weir, 2016).

This formula can be used for the quantification of immunohistochemical markers of paraneoplastic neoangiogenesis

2.5.4. Conclusions

Biological processes in any living organism are based on selective interactions between particular biopolymer chains. In most cases, these interactions involve and are driven by proteins which are the main conductors of any living process within the organism. The physical nature of these interactions is still not well known. The work presented above aims to a whole new view to biopolymer interactions, based on the assumption that these interactions are electromagnetic in their nature. So, we can consider that every biopolymer

chain has its own specific resonating frequency where the same type of receptor biopolymer can be tuned to resonate specifically by means of a electromagnetic modality, electromagnetic resonance. By doing so, a signal transduction response can invoked either by using a very little amount of ligands or without using any ligands at all, eventually obtaining the same end result therapeutically. This new theory can incorporated in the Resonant Recognition Model (RRM) developed in. The developed model is in good agreement with recent medical studies involving fractal geometry. Thus, it can be used to describe the pathological architecture of tumors and moreover, to provide information about tumor growth and angiogenesis, mechanisms complementary to those obtained by modern molecular methods.

SECTION III

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