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MULTIMODAL SURGICAL TREATMENT OF PATIENTS WITH COLUMNAR EPITHELIAL METAPLASIA OF THE ESOPHAGEAL MUCOSA

321.13 - SURGERY

Summary of the doctoral thesis in medical sciences

Chisinau, 2022

The thesis was elaborated within the Department of Surgery nr. 4, Faculty of Residency, PI State University of Medicine and Pharmacy "Nicolae Testemitanu", at the base of the surgery clinic of PMSI Republican Clinical Hospital "Timofei Moşneaga" of the Founding Consortium of the Doctoral School in the field of Medical Sciences.

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CONTENT

LIST OF ABBREVIATIONS

AC – adenocarcinoma
ADD – advanced degree dysplasia
ADE – advanced digestive endoscopy
BE – Barrett's esophagus
BMI – body mass index
EGJ – eso-gastric junction
EME – endoscopic mucosectomy
GERD – gastroesophageal reflux disease
GM – gastric metaplasia
HH – hiatal hernia
HRM – high resolution manometry
IM – intestinal metaplasia
MCE – metaplased columnar esophagus
MDD – minor degree dysplasia
SCJ – squamous-columnar junction

CONCEPTUAL REFERENCES OF THE RESEARCH

The actuality of the subject: Columnar epithelial metaplasia of the esophageal mucosa, formerly known as Barrett's esophagus (BE) or metaplased columnar esophagus (MCE), is currently a major concern problem for medical practice and science, primarily due to its evolutionary correlation with chronic gastroesophageal reflux disease (GERD), which, due to its high and continuously growing incidence in Western European countries, is considered a disease of the XXIst century. Secondly, no less important, in this respect is the potential for malignancy of the MCE with the association of dysplasia and the development of esophageal adenocarcinoma (AC) [1]. The widespread introduction of endoscopic diagnostic methods into daily practice demonstrates that MCE is a relatively common finding, with an incidence of up to 2% of all esophagoscopies and up to 10-20% of the endoscopies performed in patients with symptoms of gastroesophageal reflux disease (GERD) [2,3]. The clinical importance of MCE is determined by the predisposition to evolution complications (ulceration, hemorrhage or stricture) and especially due to the potential for malignancy, intensively studied recently. The risk of developing AC in patients with intestinal MCE has been estimated to be 30–40 times higher than in the general population [4]. The increase in the incidence of AC, especially observed in Western Europe, North America and Japan, has caused a series of controversies over the past 4 decades among surgeons, gastroenterologists and pathologists regarding Barrett's esophageal metaplasia. If, initially, the debates focused on the congenital or acquired origin of this condition, then the controversy focused on the origin of the cylindrical epithelium in the eso-gastric junction (EGJ), as well as on its histopathological aspects. An issue that has not yet been resolved among the profile specialists is referred to the definition and diagnosis of MCE. The basic criteria for its diagnosis have evolved over time, and if BE was initially considered an eponym for the syndrome that characterizes the replacement of stratified squamous epithelium with columnar epithelium, being diagnosed if the squamous-columnar junction (SCJ) was 3 cm above the EGJ, by endoscopic or histopathological examination, currently, in terms of definition, for reasons of oncological vigilance the need to consider Barrett mucosa as only MCE of specialized intestinal type [5-8] is more and more emphasized, and, in terms of diagnosis, the problem of the necessity in population *screening* programs, as well as the necessity in monitorization schemes regarding the evolution of MCE, are becoming increasingly important. Surgeons have reported a favorable response of columnar metaplastic lesions (as well as for AC prophylaxis) to the surgical treatment of reflux, ablative surgical treatment of metaplasia, compared to continuous antacid therapy, but this still remains a controversial issue [9 - 11]. Antisecretory medication appears to be effective in eliminating GERD symptoms, but its long-term application may cause adverse reactions, a negative therapeutic cost/efficacy balance, and the potential for reversibility of MCE in normal anatomical-physiological conditions/neoplastic progression is discussed.

The medical-surgical approach of MCE at national level, in medical institutions, involves a different diagnostic-curative attitude, dependent on several factors (lack of a standardized national protocol, different technical possibilities, etc.). Early diagnosis of MCE with the study of the genetic markers, of the data collected in the field of immunohistopathology and genetic engineering, the endoscopic examination by advanced digestive endoscopy methods are still in their early stage. The absence at national level of a clear diagnostic-curative algorithm, as well as of specialized studies on diagnostics and treatment tactics, as well as the need for large-scale implementation of new methods of diagnosis and minimally invasive, multimodal treatment, are the considerations that induced us to choose MCE as a study direction. The results of this study

related to the field of research were used in publications, articles and the development of a diagnostic-curative guideline for practitioners.

The purpose of the study:

Optimizing the treatment results of the patients with columnar epithelial metaplasia of the esophageal mucosa by implementing contemporary diagnostic methods (endoscopic and histopathological) and developing an optimal algorithm for multimodal medical-surgical treatment of the patients with this disease.

Objectives of the study:

1. Comparative assessment of the diagnostic value of clinical data (symptomatology), imaging methods (advanced digestive endoscopy) and functional methods (high resolution manometry and esophageal pH-metry) in establishing the positive diagnosis of columnar epithelial metaplasia of the esophageal mucosa.
2. Implementation in clinical practice of new diagnostic methods: advanced imaging, functional and immunomorphological methods.
3. Analysis of the risk of neoplastic progression of columnar epithelial metaplasia by histopathological and immunohistochemical examination.
4. Comparative analysis of different treatment methods in the columnar epithelial metaplasia of the esophageal mucosa and the widespread introduction of minimally invasive, staged (endoluminal and laparoscopic) techniques for the treatment of this pathology.
5. Determination of the groups of patients with columnar epithelial metaplasia of the esophageal mucosa for treatment, supervision (clinical and endoscopic) and clinical evaluation of the treatment applied using the pre- and post-therapeutic quality of life assessment score.
6. Development of a complex algorithm for the diagnosis, *screening* and treatment of patients with columnar epithelial metaplasia of the esophageal mucosa.

Research methodology: The thesis is an analytical, experimental, clinically controlled study, whose field of research was the evaluation of the clinical-paraclinical particularities, diagnosis and treatment of patients with chronic forms of GERD complicated by MCE in a group of 61 patients. Classical, traditional methods were used in the clinical-paraclinical examination (general blood and urine tests, biochemical tests, ECG, esophagus radioscopy with BaSO4, standard upper GI endoscopy (EGD)), as well as new diagnostic methods: advanced digestive endoscopy: advanced narrowband endoscopy (NBI^{+}), magnification endoscopy by *Near Focus* technology, high resolution esophageal manometry (*HRM*), diurnal esophageal pH-metry, as well as morphopathological (bioptic) and immunohistochemical examination of the MCE. The surgical treatment of these patients was focused on the combination of minimally invasive surgical techniques in a staged manner: endoluminal (resection or ablative treatment of the metaplastic mucosa) and laparoscopic antireflux techniques. The treatment of the complicated forms of MCE (stenosis, advanced dysplasia/neoplasia) underwent classical surgical treatment - esophagoplasty.

Theoretical and practical significance: The work presents a unique study in our country, which analyzes MCE as a whole: the progressive clinical-paraclinical particularities of the patients with MCE and the need for its surgical correction were assessed. The value and diagnostic accuracy of different paraclinical methods in establishing the diagnosis were assessed by comparison, the indications for the surgical interventions for different forms of metaplasia were established, as well as the type necessary for the eradication of the pathological substrate. Different methods of surgical treatment have been compared in terms of immediate and late results.

Classical, laparoscopic and endoluminal surgical treatment techniques were analyzed and new ways of effectively performing these surgical interventions were proposed. Immediate and late postoperative results were analyzed and an optimal algorithm for the diagnosis and treatment of MCE was developed.

Approval of the scientific results: The annual scientific conference of the scientific-teaching staff, doctoral students, master students, residents and students of SUMP "Nicolae Testemitanu" October 18-21, 2016; National Surgery Conference, XVIIIth edition, October 4-7, 2017, Iasi, Romania; National Congress of Surgery, Iasi, Romania, April 16-19, 2017; VIth International Scientific and Practical Conference "Actual Issues of Modern Medicine" Baku, Azerbaijan, May 3-5, 2017; VIIIth annual scientific and practical conference of young scientists of the Federal State Budget Educational Institution for Additional Professional Education "Russian Medical Academy of Continuous Professional Education", Moscow, Russia, March 16-19, 2017; XIIIth Edition of AGEPI Readings, Chisinau, April 19-20, 2017; Ist SURGICAL FORUM OF BUKOVINA, Chernivtsi, Ukraine, September 28-29, 2017; National Surgery Conference, XXIXth edition, Sinaia, Romania, June 6-9, 2018; SUMP Annual Scientific Conference "Nicolae Testemitanu", Chisinau, October 16-18, 2018; IInd SURGICAL FORUM OF BUKOVINA, Chernivtsi, Ukraine, September 23-26, 2018; XIVth Edition of AGEPI Readings, Chisinau, April 24-26, 2018; Forum of the Association of Surgeons of the Republic of Moldova, November 30, 2018; National Surgery Conference, XXXth Edition, Craiova, Romania, May 7-10, 2019; SUMP Annual Conference "Nicolae Testemițanu", October 15-18, 2019; XIIIth Congress of the Association of Surgeons "Nicolae Anestiadi" and the IIIrd Congress of the Society of Endoscopy, Minimally Invasive Surgery and Ultrasonography „V.M. Gutu" of the Republic of Moldova, Chisinau, Republic of Moldova, September 18-20, 2020; National Surgery Conference, XXXIst edition, Sinaia, Romania, November 4-7, 2020.

At the elaboration of the research project, the Positive Approval of the Research Ethics Committee within the PI State University of Medicine and Pharmacy "Nicolae Testemitanu" was obtained - protocol nr. 73 from 17.06.2016. The results of the thesis were discussed and approved during the meeting of the Department of Surgery nr. 4 of the State University of Medicine and Pharmacy "Nicolae Testemitanu" - protocol nr. 3 from 02.03.2022 and the meeting of the Scientific Surgery Profile Seminar 321.13 of the State University of Medicine and Pharmacy "Nicoale Testemitanu" - protocol nr. 1 from 18.03.2022.

Publications on the subject of the thesis: The thesis materials were reflected in 45 specialized publications, 14 articles: of which articles cited SCOPUS - 3, articles in recognized foreign journals - 1, articles in journals from the National Register of profile journals - 8; of which: articles in accredited national scientific journals: type B - 6, articles in national scientific collections - 2, articles in international scientific collections - 1, articles in the works of international scientific conferences, held in the Republic of Moldova - 4. Number of single author publications - 4. Conference materials/theses: international - 25, national with international participation - 5 and 16 oral communications at national and international specialized forums. There are 3 ideas related to the research topic which were patented and 15 proposals for the rationalization of operating techniques which were registered.

Summary of the thesis compartments: The thesis includes annotations in Romanian, Russian and English, a list of abbreviations, introduction, 4 chapters, discussions and synthesis of the obtained results, general conclusions and practical recommendations, bibliography, appendices, the statement of responsibility, the candidate's CV.

THESIS CONTENT

1. **Evolution of the concept of columnar epithelial metaplasia of the esophageal mucosa** (literature review) represents the analysis of recent specialty literature data (synthesis being performed by processing databases such as: PubMed, Embase, WorldWideScience.org, DOAJ, SpringerLink, Academic Journal Database) regarding the MCE issue. Brief historical data on the evolution in time of the notion of esophageal metaplasia and its notorious efferent findings are presented. Epidemiological data and the main risk factors for the development of the metaplastic substrate of the esophagus are analyzed in the second part of the chapter; in relation with them, the clinical manifestation of the disease and its possible consequences were characterized. The following describes in detail the histopathogenetic mechanisms and analyzes the theories of development and evolution with emphasis on the 2 histological types of MCE: gastric metaplasia (GM) and intestinal metaplasia (IM). The data are exposed in terms of genetic, immune and histological changes. In the third part of the chapter, the data of the international guidelines and protocols for the *screening* and supervision of the patients with MCE are clearly presented.
2. **Clinical material and methods of research.**

The research project was carried out within the Department of Surgery nr. 4, Faculty of Residency of the State University of Medicine and Pharmacy "Nicolae Testemitanu", head of the department Dr. habilitated in medical sciences, associate professor, Ungureanu Sergiu. The thesis represents an analytical, experimental, clinically controlled study that had as field of research the evaluation of the clinical-paraclinical particularities, diagnosis and treatment (according to a diagnostic-curative algorithm established in the study) in patients with refractory GERD, complicated by MCE.

The representative research group was calculated in the EpiInfo 7.2.2.6 Program, "StatCalc-Sample Size and Power" section, based on the following parameters: confidence interval for 95.0% significance of the results; statistical power - of 80.0%; the difference in effect between the research group and the control group is 18.0%.

Ratio between the groups - 1:1, adjustment to the non-response rate, estimated at 10.0% (q = 1/(1-f)).

Result: 54 patients with columnar epithelial metaplasia of esophageal mucosa.

Thus, the prospective research group requires a sample of at least 54 patients for the representativeness and comparability of the new medical-surgical approach. In our project, it included 61 patients with MCE diagnosed and treated in the Surgery Clinic nr. 4 of PMSI Republican Clinical Hospital "Timofei Moşneaga" during the years 2016-2019.

The inclusion criteria of the patients in this research were: the presence of the diagnosis of MCE, histopathologically confirmed, in patients of both genders, aged 18-80 years, who accepted the study conditions and signed the informed consent of participation in the research project.

The exclusion criteria were the following:

- Patients with decompensated somatic diseases:
  - cardiac: heart failure degree IV NYHA,
  - acute or recent myocardial infarction,
  - stage III-IV cancer patients with a location other than EGJ,
  - patients with esophageal AC without MCE,
- Patients with MCE who did not accept the conditions for participation in the study,
- Vulnerable patients,
- Patients who refused to continue participating in the study at various stages of the research

process by refusing the diagnostic-curative procedures established in the project.

On the other hand, taking into account the fact that according to some international supervision guidelines, some of the patients diagnosed with MCE (gastric type), without the association of dysplastic complications, benefit from drug treatment in the first therapeutic stage, a control group was created (statistically comparable, 61 cases) of patients confirmed with MCE and who received only medicinal treatment (according to the standard study protocol) in 78.3% of cases (with PPIs, prokinetics, gastric bandages and diet) or without medicinal treatment (21.7 %), being followed and re-evaluated clinically and paraclinically, during the same period of the study, for analysis and comparability and which constituted the supervision group.

In order to identify the characteristics of the patients with GERD symptoms in both research groups, we performed a statistical processing of the data presented at the primary examination, and the evaluation was performed by collecting the anamnesis and the diagnostic imaging data. Completing the "*GERD-Health Related Quality of Life Questionnaire*" (HRQL, Velanovich V. The development of the *GERD-HRQL* symptom severity instrument. Dis Esophagus 2007;20: 130-4) was the tool for assessing patients' quality of life at the time of access to the research project and at the stages after the endoluminal and laparoscopic antireflux surgical treatment in order to assess the postoperative results.

The study included patients aged 18-80 years (Table 1).

Table 1. **The age ratio of the patients included in the study**

Age	Women		Men		Total	Frequency	P value
<19 years	-	-	1	2.56%	1	1.63%	t-test, p=0.005
19-35 years	2	9.09%	19	25.64%	11	19.67%	
36-50 years	7	31.81%	15	38.46%	22	36.06%	
51-60 years	8	36.36%	10	25.64%	18	29.5%	
>61 years	5	22.72%	4	10.25%	9	14.75%	

The number of men included in the research group (39 cases) was higher than that of the female group (22 cases) and is consistent with the literature data [12]. Among the total group of patients with MCE, 36 (59.01%) of patients were young and 25 (40.98%) of patients, which constituted more than 1/3 of the research group, were patients who were > 50 years old. The predominantly affected age was the fourth and fifth decade, and the average age of the patients included in the research group was 45.12 ± 1.72 years (95% CI 40.72 - 47.26). According to the gender division of the patients involved in the research project, a ratio of 1:1.4 with the predominance of men was registered. According to the history of the disease, the duration of the disease varied between 1 and 15 years, and on average it constituted 3.03 ± 4.78 years (95% CI 1.97–7.23), 40.98% (25 patients) among them were patients receiving specific systematic gastroprotective and antacid treatment, 31.14% (19 patients) - intermittent treatment, and 19.67% (12 cases) of patients were chronically consulted patients (sometimes even more than 5 years) in various public medical sanitary institutions without establishing the clinical diagnosis. The onset of the disease was generally slow, documented with signs of GERD for several years (> 1 year) in over 88.5% (54 cases) of patients in the research group and in 63.9% in the control group (p_value 0.001 Chi-Square test). Among the specific clinical signs of GERD, the most common in the research group was heartburn - 83.6% (51 cases), postprandial eructations and retrosternal discomfort, which were present in 40.98% (25 cases) and 45.90% (28 patients) of cases respectively, and from the extraesophageal symptomatology, most frequently MCE was associated with rhinolaryngological signs, attested in 14.75% (9 cases).

Concomitant pathology was attested in about 1/4 of the total number of patients involved in the research group. In this case, MCE was most frequently associated with HH (42.62%, 26 cases), in about 26% (7/26 patients, t-test) of the cases, they were large, mixed hernias; 34.61% (9 cases) were axial type HH and 15.38% (4 cases) - HH by sliding (p_value 0.003 Chi-Square test). In 29.5% (18 patients) there was GERD with marked GER, appreciated in paraclinical examinations. Obesity was associated in 13.11% (8 cases), most frequently these patients were overweight with a body mass index (BMI) of 28-30 and accounted for 22.95% (14 cases), and stomach ulcer disease was present in 6.5% (4 cases) of patients involved in the research group (p_value 0.001 Chi-Square test).

General paraclinical examinations.

All the patients included in the research project, in order to confirm the diagnosis of GERD complicated with MCE, were subjected to laboratory tests (multiple standard hematological and biochemical systemic parameters, performed by means of automatic and semi-automatic analyzers), performed in the biochemical laboratory of PMSI Republican Clinical Hospital "Timofei Moșneaga", and to EGJ-specific paraclinical examinations (endoscopic, histopatomorphological, immunohistochemical and functional: monometry and diurnal esophageal pH-metry), performed in medical institutions properly equipped for this purpose (Advanced Digestive Endoscopy Laboratory (ADEL), MC Excellence, and PMSI Clinical Hospital of the Ministry of Health of the Republic of Moldova, SYNEVO Pathomorphology Laboratory).

Upper GI endoscopy (EGD)

In the research project, for diagnostic purposes EGD was used to examine the esophagus, EGJ, stomach and to characterize MCE, precancerous lesions and early cancer on this background. There were differentiated 2 qualitative levels for the endoscopic examination: the ***standard level***, which included general methods for the stage of detection of EGJ pathologies and the ***expert level***, which included advanced methods, used for the stage of characterization of detected lesions and conditions. Endoscopic examination in white light was the primary stage of diagnosis, being further followed by endoscopy with expert techniques (Figure 1).

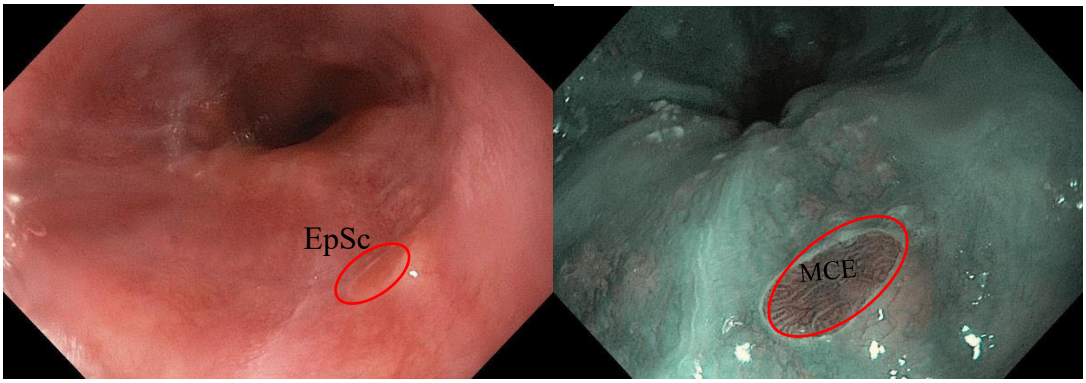

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Figure 1. **Endoscopic examination of MCE in:**
a) standard regimen; b) expert regimen (*NBI*$^{+}$, *Near Focus*)

The standard level used high-resolution white light endoscopy without any special additional techniques. The expert level was completed with narrowband endoscopy (*NBI*$^{+}$), high image resolution, close focus, optical and digital magnification, when needed chemical chromoendoscopy was used, associated with the magnification and electronic chromoendoscopy techniques.

Endoscopic evaluation of the MCE segment length was performed according to the *C&M* Prague criteria (circumferential extension C and maximum extension of the metaplasia segment M). In the research group, the endoscopic examination at expert level allowed the visualization of the foveolar *pattern* (Figure 2), making a concordance between the characteristics of Guerllud [13,14] and the histopathological aspects.

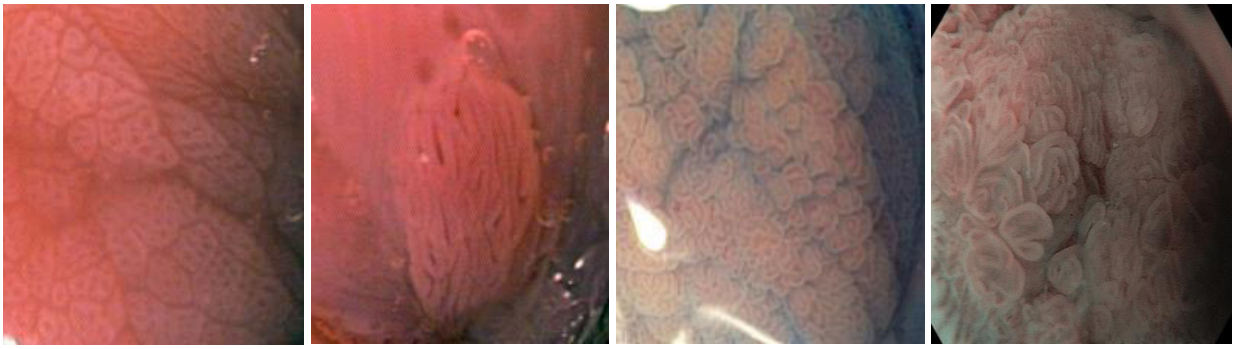

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Figure 2. **Guerllud classification. Endoscopic aspect.**
a) Type I-Round, b) Type II-Reticulated, c) Type III – Villous, d) Type IV - Dentate

Advanced EGD techniques combined with chromoendoscopy techniques were used to detail the superficial appearance of the suspicious mucosa and to determine the precise surface extension. For this purpose, the examined mucosa was sprayed with chromoendoscopy agents through the Pauldrach 123-354-02 axial *spray*-catheter, diameter 2.3x1600 mm.

Multiple biopsies were performed for biopsy confirmation, exclusion of dysplasia and malignancy, being layered according to Seattle recommendations: in 4 quadrants at every 2 cm from the metaplasia for segments larger than 3 cm and at every 1 cm for segments smaller than 3 cm. In comparison, the advanced EGD techniques *NBI*$^{+}$, through the images they offer, allow targeted, optically guided biopsy - *"target"*. (Figure 3)

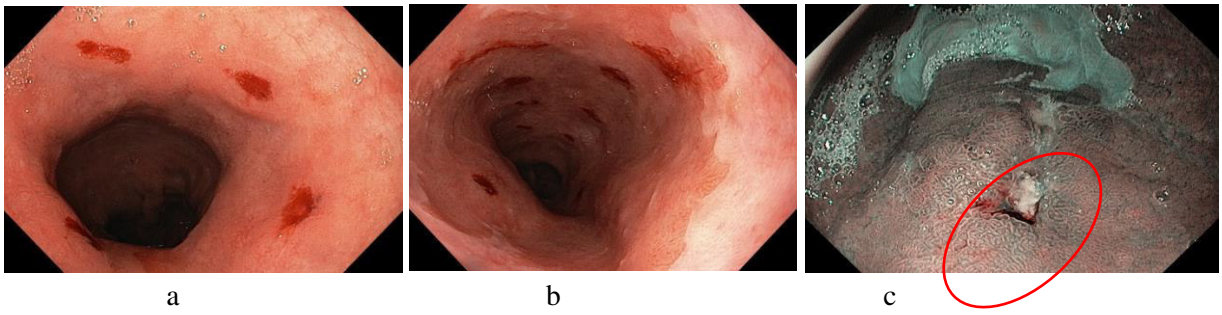

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Figure 3. **MCE biopsy: a,b) Seattle protocol in 4 quadrants; c) „*target*" - biopsy**

The associated inflammatory lesions of the esophageal mucosa, highlighted in EGD, were manifested by esophagitis (57.7% in the research group and 52.1% in the control group) and ulcerations (3.9% in the research group and 5.2% in the control group). The severity of the mucosal lesions was assessed using the *Los Angeles* Endoscopic Classification.

Barium radiological examination

The sensitivity of this examination remains low for the diagnosis of MCE, especially if it is not associated with a complication or if another pathology does not coexist (more commonly HH or GERD). In the research group, it was applied in 98.3% (60 cases). This allowed the evaluation of the anatomical changes (erosions, ulcers, strictures, stenoses, HH, etc.), as well as of the functional disorders of the esophagus (esophageal *clearance*, GER and motility disorders).

Histopatomorphological examination

The histopatomorphological examination was performed in all cases by double control, by 2 histopathologists: in the morphopathology department of PMSI Republican Clinical Hospital "Timofei Moşneaga" and by Vitalie Tirbu, pathologist, head of the Histology Laboratory, Synevo Medical Laboratory (Figure 4).

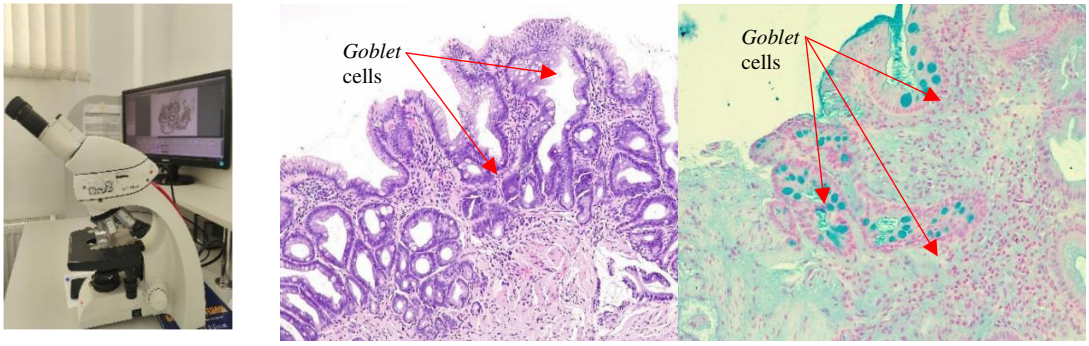

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Figure 4. **Histopathological examination of MCE:**
a. Leica ICC 50 E microscope, FusionOptics™,
b. H&E coloration, c. Alcian Blue coloration

Particular attention was paid to the histopathological interpretation of MCE in terms of the three types of epithelium described primarily in 1976 by Paull A., Trier SJ et al. [3]: junctional, fundic or intestinal, but also to the pathognomonic histopathological changes for a MCE with neoplastic progression - dysplastic changes discussed in the light of the Vienna classification [15]. The histopathological result was the one that dictated the medical-surgical approach of the patients included in the research group.

Immunohistochemical examination

In the clinic, the morphopathological examination during the recent years has been supplemented by the immunohistochemical examination of the patients, and this is because the method is not provided for by the national medical insurance company, and the procedural costs are quite high. Another cause of the attention deficit for the immunohistopathological examination in the first half of the project was determined by the fact that a large part of the immunohistochemical biomarkers for MCE, IM (still in various stages of research) are not fully recognized for use in the clinical practice.

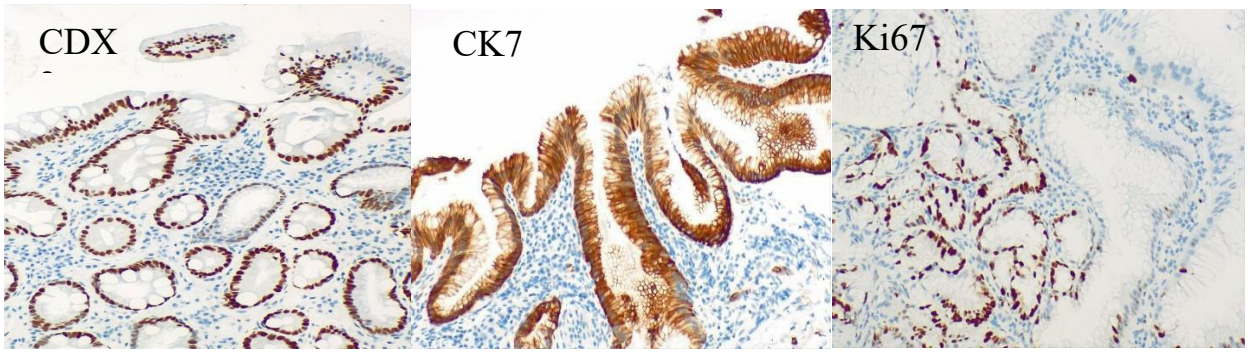

Figure 5. **Immunohistochemical diagnosis in MCE with IM**

Given the low rate of neoplastic progression in BE and the inherent limitations of the current endoscopic supervision programs, there has long been interest in identifying the biomarkers of risk for neoplastic progression in Barrett patients. Within the project, using data from the literature, we created a panel of biomarkers for immunohistochemical examination of the patients in the pre- and

post-ablation period of MCE. 20 patients underwent immunohistochemical examinations: 10 cases with IM and 10 cases with GM. These were immunohistochemically examined by 8 markers: CK7, CK20, Ki67, EMA, CDX 2, p53, HER 2, AMACR (Figure 5).

Over time, many biomarkers have been studied for patients with BE, but even more so for patients with esophageal AC, we tried their analysis in terms of comparative immunohistochemical examination in two conclusive research groups to analyze the risk of neoplastic progression. Thus, within the research project with the support of Professor Silviu Constantinoiu, head of the Center of Excellence in Esophageal Surgery, St. Mary's Hospital, Bucharest, Romania, a study was performed to compare the specific immunohistochemical markers of esophageal AC, developed on the basis of IM of the esophageal mucosa (20 cases, group I) opposite the immunohistochemical markers investigated in our research group in 20 patients with MCE - 10 patients with IM and 10 patients with GM (group II), respectively. Although several factors were investigated in separate groups, only 5 immunohistochemical factors (CK7, CK20, CD X2, p53 and Ki 65) could be analyzed in the comparability study in these two groups. The criterion for their analysis was the method of immunohistochemical examination, as well as the same reading value of the result (positive/negative, the degree of expression in percent).

Diurnal pH-metric examination.

In the study, esophageal pH-metry, performed using *Orion II, MMS,* Netherlands (Figure 6a) and esophageal manometry with Solar *GI HRM MMS*, Netherlands (Figure 7a) as part of the diagnostic process estimated the degree of the lower esophageal sphincter (LES) incompetence, type of GER, types of esophageal motility, as well as esophageal *clearance*, and consequently they served as a criterion for assessing the pattern of laparoscopic fundoplication applied in the antireflux surgical stage to our patients.

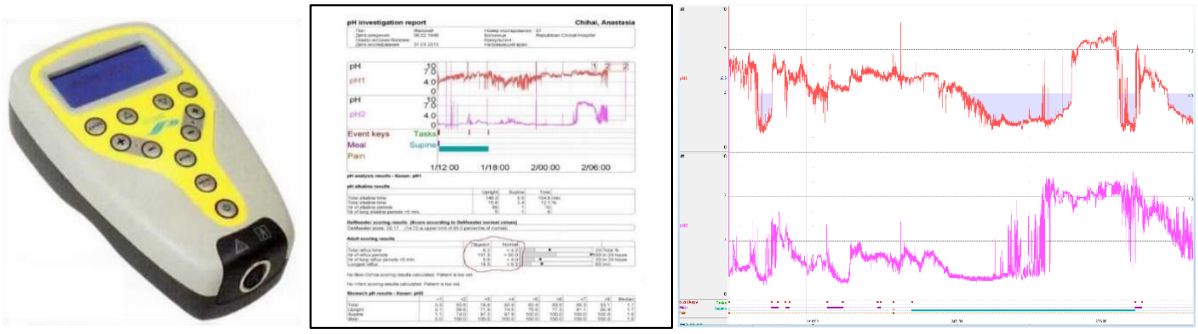

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Figure 6. **a) pH-meter Orion II, MMS, Netherlands; b) pH-metric examination of GERD.**

In the research group, diurnal esophageal pH-metry was applied to 48 patients with MCE: 22 women and 26 men; average age 45.75 ± 10.13 years (95% CI 43.37 - 42.16).

Examination of the eso-gastric motility

Esophageal manometry allows the assessment and analysis of the indicators of esophageal muscle motility, as well as the functionality of its sphincters. Compared to conventional manometry, high-resolution manometry (*HRM*), used in our research project, has a higher number of sensors (24), located at a shorter distance one from each other and has a higher diagnostic accuracy (Figure 7).

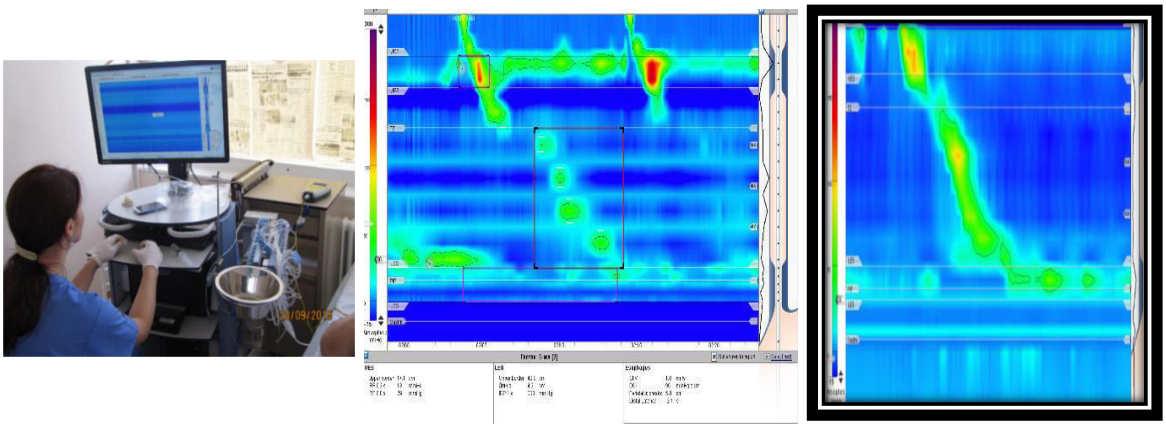

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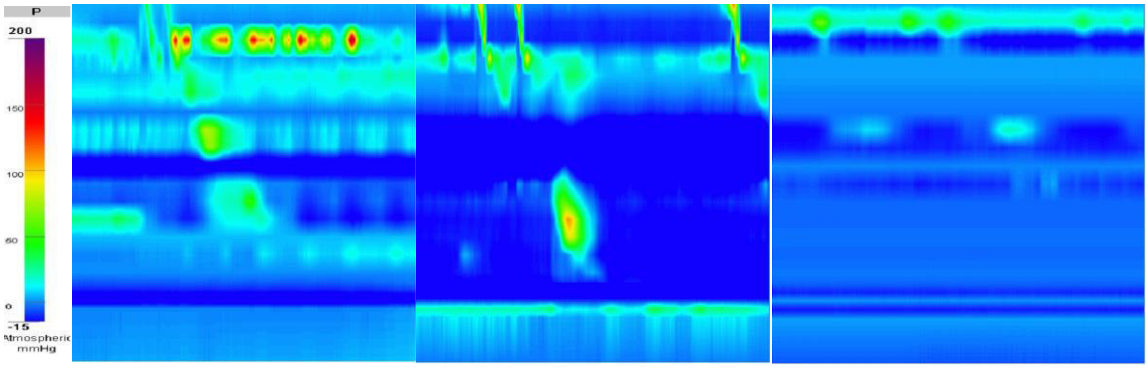
Figure 2.7 **a) High-resolution manometer Solar GI HRM MMS, Netherlands b) Manometry results in GERD**

Advances in high-resolution manometry have revolutionized the clinical assessment of esophageal motility disorders, and interpretation by *HRM* nowadays may replace conventional manometric systems as a standard diagnostic tool in the assessment of non-obstructive esophageal motility disorders.

The manometric characterization of esophageal motility disorders in the study was based on four models of esophageal motility (Figure 8):

- Normal esophageal peristalsis is defined by the presence of > 50% successful swallowings, associated with a normal relaxation of the LES.
- Ineffective esophageal motility or peristalsis pattern, characterized by > 50% normal swallowings and a DCI (distal contractile integral) < 450.
- Fragmented peristalsis, the presence of > 50% of successful swallowings, with a DCI > 450, but with the presence of axial breaks greater than 5 cm in the isobaric contour of 30 mmHg.
- Absent peristalsis (major motor disorder), characterized by the normal relaxation of the LES, but with the total absence of esophageal muscle contractility defined by DCI < 100.



a b c

Figure 8. **Patterns of esophageal motility: a) fragmented peristalsis, b) ineffective peristalsis, c) absent peristalsis**

Mathematical-statistical methods used in the study

The statistical processing of the results was performed according to the rules of variable statistics and probability theory, following the widely used methods. The representative research group was calculated in the EpiInfo 7.2.2.6 Program, "StatCalc-Sample Size and Power" section. The probability value was assessed according to the t-Student criterion. A $p \geq 0.5$ was considered as a

conclusive statistically significant criterion. In order to determine the interdependence between the changes of the studied indices, a correlational analysis was performed, calculating the Pearson correlation coefficient (r). The r value from 0 to 0.3 defined a weak correlation between the comparison indices; from 0.3 to 0.7 - a moderate correlation and from 0.7 to 1 - a strong correlation. The obtained results were statistically processed based on the Excel program, using the personal computer based on the Intel Pentium V processor. The significant difference between the indices was determined based on the Fischer-Student table of values, Likelihood Ratio test, Chi Square test. The diagnostic value of the immunohistochemical markers was analyzed in terms of ROC curves. In order to assess the interdependence of causal factors and specificity for esophageal dysmotility we performed a comparative analysis of the study groups using the exact Fischer tests for qualitative data, the t-Student test or a non-parametric Mann-Whitney test when the t test could not be applied for quantitative data, then we performed a multifactorial analysis to study the factors associated with MCE using the logistic regression analysis. The assessment of quality of life indices by the HRLQ questionnaire was statistically analyzed by the Kruskal-Wallis test and the McNamer test.

3. Classical and modern approaches in the diagnosis of patients with columnar epithelial metaplasia of the esophageal mucosa.

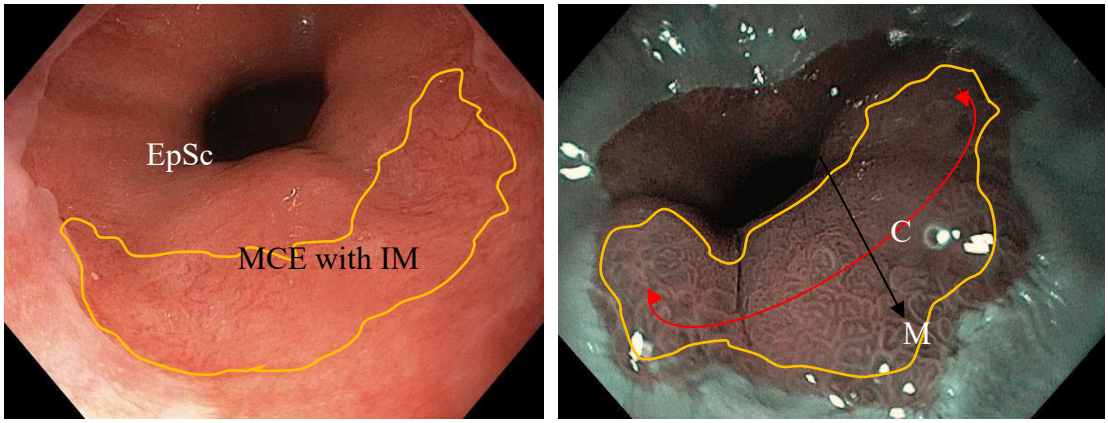
3.1 Clinical aspects of the evolution of columnar epithelial metaplasia of the esophageal mucosa and the role of advanced digestive endoscopy in its diagnosis

The symptoms of uncomplicated MCE and GERD are largely similar (heartburn, regurgitation, retrosternal discomfort, odynophagia), except for the phase of complications: ulcer, stenosis, hemorrhage or malignant degeneration. Thus, as a crucial moment of caution in establishing the early diagnosis of MCE is the detection and supervision of patients with GERD [3,14,16]. Although not all the patients diagnosed with MCE have a certain degree of esophagitis at the primary diagnosis, it is certain that etiopathogenetically the metaplastic changes are preceded by evolutionary stages of esophageal inflammation caused by GER. All the patients in the research group were known to have heartburn for more than 8.3 ± 4.1 months (95% CI 6.9-9.7), and 16.39% (10 cases) of them had a disease duration older than 10 years. Although GERD is most commonly complicated by esophagitis, EGJ ulcers have been diagnosed more and more frequently. Barrett's ulcer occurs in 14-24% of patients with MCE, associated with chronic and permanent GER, and the reflux in this case can cause upper GI hemorrhage, penetration, esophageal stenosis, perforation with mediastinal fistula and mediastinitis [17]. In the research group, Barrett's ulcer was attested in 4 cases, p_value 0.001 Fisher test (all attested on IM). 4 patients were diagnosed with stenotic complications. These patients required a multidisciplinary approach, underwent laborious surgical interventions, and eventually became the cases which registered major postoperative complications and postoperative mortality.

Upper GI endoscopy in columnar epithelial metaplasia in the distal esophagus

EGD with endoscopic biopsy and histopathological examination, in complex, establish the diagnosis of MCE and Barrett's esophagus. The endoscopic examination in MCE determines the following criteria: the presence of MCE and the length of the metaplasia segment in the distal esophagus; appreciation of the shape of the metaplasia extension as circumferential (criterion C), maximum (criterion M) and appreciation of the length of each criterion; ascertaining the presence of HH with its typification and gradation; characteristics of the associated pathological changes of the mucosa in the distal esophagus and the junctional area (inflammation, erosions, ulcers);

assessment of the structure of the metaplastic epithelium (typing, foveolar *pattern* and vascular *pattern*, delineations, depressions and elevations, granular and nodular masses) suspecting, confirming or excluding stigmas of minor grade dysplasia (MGD), advanced grade dysplasia (AGD), early neoplasia, invasive neoplasia. The currently recognized international standard for the endoscopic assessment of the extension of columnar metaplasia in the distal esophagus is represented by the *Prague C&M* criteria (Figure 9) [18].



a b

Figure 9. **C&M Prague criteria for MCE in regimen of:**
a) White light EGD; b) *NBI*⁺ EGD; c) *pitpattern* expert evaluation

According to the C&M Prague classification, MCE extension in the surface of the esophageal mucosa in the research group was as follows (Table 2):

Table 2. **Distribution of patients in the research group according to C&M Prague criteria**

C&M Prague criteria	**C0M1**	**C0M2**	**C0M3**	**C0M4**	**C1M3**	**C1M4**	**C1M5**	**C2M4**
Nr. of cases	*4*	*3*	*5*	*9*	*16*	*17*	*4*	*3*
Frequency (%)	6.55%	4.91%	8.1%	14.75%	26.22%	27.86%	6.55%	4.91%
P value	ns Fisher test =0.001							

Among the 61 patients included in the research group, 39 were patients whom endoscopy detected MCE "in flame-like tongues", 8 cases of circular MCE, and 14 cases presented mixed forms of metaplastic epithelium extension on the esophageal mucosa. The maximum length of the MCE was 13 cm.

Advanced EGD methods allow reducing the area for biopsy, reduce the number of biopsies and increase the efficiency of the procedural costs. A randomized, crossover study determined that *NBI*⁺ reduced the number of biopsies per patient (3.6 vs. 7.6, p <0.001) and increased the rate of detection of the dysplastic areas (30% vs. 21%, p = 0.01). [19]. On this basis, in the study we used *NBI*⁺ as a stratifying tool for biopsy, where areas with regular *pitpattern* and *vascular pattern* were left safe and unbiopsied, and areas with changes in the foveolar architecture and dysregulated and atypical microvascular changes were biopsied by endoscopic optical guidance. Chemical chromoendoscopy in the research group was applied as an adjuvant method for additional characterization and detailing: in 32.3% of cases by local transendoscopic spraying of 1.5% acetic acid solution, methylene blue solution and 0.4% indigocarmin solution. Lugol solution was used in order to clearly clarify the boundaries of MCE extension in the squamous surface, in the electronically difficult cases (4 cases). Chromoendoscopy improved the endoscopic

microstructural detailing of the metaplased mucosa in 21 cases and concretized the boundaries of extension (4 cases), favoring the optically guided biopsy of the mucosa with concrete pathological changes (p_value = 0.01, Fisher test). The *NBI*$^{+}$ technique increased the rate of MCE detection, detailing and endoscopic characterization of its complications in 90.3% (p_value = 0.01, Fisher test) of cases and favored the examination of the foveolar pattern (*pitpattern*) and vascular microarchitectonics (*vascular pattern*). The classification of the *pattern* according to Guerllud in the research group appreciated the following microstructure of the MCE (Table 3):

Table 3. **Endoscopic expression of the foveolar *pattern* of MCE in the study**

Foveolar *pattern*	**Nr. of cases**	**Relative frequency (%)**	**P value**
I – Round	7	11.47%	P_value =0.003 Fisher test
II – Reticulated	17	27.86%	
III – Villous	21	34.42%	
IV – Dentate	16	26.22%	
Total	61	100%	

In the process of endoscopic examination we noticed that specialized IM was characterized in 82.7% of cases by villous and dentate foveolar pattern, which were directly proportionally associated with distorted, irregular vascular patterns and which were found in a proportion of 60.64% of cases (p_value = 0.001, Fisher test).

3.2 Diagnosis of esophageal motility and gastric secretion disorders in patients with columnar epithelial metaplasia of the esophageal mucosa

In the research group, the manometric examinations were performed mainly in the preoperative period in order to assess the esophageal motoricity, the degree of LES damage and finally to assess the type of sleeve required in the antireflux surgical stage. In about 32% of cases (11 patients) there was a prolonged DL, and in 16% (6 patients) - a marked DL. Fragmented peristalsis occurred in 10 patients (21.7%) of the total number of patients examined, and ineffective peristalsis (DCI < 450) - in 15 cases (32.6%). The average LES pressure < 6 mmHg was assessed in 7 patients (22%), in 6 patients (19%) the LES pressure was < 10 mm Hg. In the study we performed a comparative analysis of the research groups using exact Fischer tests for qualitative data, t-Student test or a non-parametric Mann-Whitney test when the t-test could not be applied, for quantitative data. This analysis allowed us to show that the presence of esophageal motility disorders was a factor independently associated with MCE with: PR 3.9; 95% CI 1.7-9.3; p = 0.001. The presence of H. pylori in gastric biopsies and the presence of HH were 2 other factors that were significantly associated with the presence of MCE (respectively PR 0.08; 95% CI 0.008-0.84; p = 0.035 and PR 5.60, 95% CI 2.45-12.76; p <0.001). The other factors studied were not significantly associated with MCE. Some patients with MCE have low esophageal sensitivity to pain due to the sensitivity threshold and mucin protection of the goblet cells, and as a result, gastro-duodenal reflux into the esophagus may not be clinically manifested, but it may be pH-metrically assessed. In our study, pH metrics was applied to 48 patients (78.68%). According to the DeMeester score, in 28 patients (58.3%) a score of > 16 was calculated, in 35.7% (10 cases) of these patients the GERD was assessed as mild, 21.4% (6 cases) as a moderate form, and in 42% of cases (12 patients) there were severe forms of GERD. Following the pH-metric examination, the results were correlated with the severity of the esophageal mucosa lesions obtained at endoscopic examination (Table 4).

Table 4. **Correlation of the reflux type and reflux esophagitis in the study**

Reflux type	Reflux esophagitis		Total	P value
	Stage A-B	Stage C-D		
Acid	18 (60%)	5 (41.6%)	26 (61.9%)	0.307 (Likelihood Ratio)
Alkaline	4 (13.3%)	4 (33.3%)	6 (14.2%)	
Mixed	8 (26.6%)	3 (25%)	12 (28.5%)	
Total	30 (100%)	12 (100%)	42 (100%)	

Radiological diagnosis is suggestive only when complications occur or if HH and/or GER are associated. During the study, GER at barium examination was demonstrated in 41 patients (67%) and predominantly attested in patients with IM (71%, 29/41 cases). HHs were more common in patients with GM (16 cases, 57%), and radiologically correlated with a constant GER in these patients: 12 cases out of 16 patients with HH associated with GER (Table 5).

Table 5. **Barium radiological examination in patients with MCE in the research group**

MCE	No dysplasia	MGD	AGD	Esophageal AC	GER at radiological barium examination	HH at radiological barium examination	P value
IM	30 (49.18%)	9 (14.75%)	2 (3.27%)	2 (3.27%)	29 (47.54%)	13 (21.31%)	0.401 (Likelihood Ratio)
GM	9 (14.75%)	7 (11.47%)	2 (3.27%)	-	12 (19.67%)	16 (26.22%)	
Total	61 (100%)				41 (67.21%)	29 (47.54%)	

3.3 Histopathological and immunohistochemical diagnosis in columnar epithelial metaplasia of esophageal mucosa

The diagnosis of MCE is confirmed histopathologically, by demonstrating the existence of one of the 3 known types of epithelium: 1. fundic-type epithelium, with mucus secretory cells, parietal and oxyntic cells; 2. foveolar-looking junctional epithelium and with mucus-secreting cells; 3. intestinal epithelium of villous appearance with mucus-secreting cells and goblet cells [14,20]. Histopathologically in 24 patients (39.34%) epithelial metaplasia of fundic or junctional type (GM) was confirmed and in 37 patients (60.65%) IM was confirmed, 1 case of MCE at the histopathological examination showed both metaplastic epithelium specific to the gastric mucosa, but also goblet cells. More than 91% of the patients (55 cases) in the study were diagnosed at an early stage of the disease, without the association of dysplastic complications, or had a MGD.

Table 6. **Association of the foveolar *pattern* with MCE forms in the study**

Foveolar *pattern*	**Epithelial metaplasia type**			Total	P value
	Fundic	Junctional	Intestinal		
I -Round	2 (3.27%)	2 (3.27%)	3 (4.91%)	7 (11.47%)	p_value =0.004 (Likelihood Ratio)
II - Reticulated	-	5 (8.19%)	5 (8.19%)	10 (16.39%)	
III - Villous	-	8 (13.11%)	13 (21.31%)	21 (34.42)	
IV - Dentate	-	7 (11.47%)	16 (26.22%)	16 (26.22%)	
Total	2 (3.27%)	22 (36.06%)	37 (60.65%)	61 (100%)	

Among the 6 cases of AGD, in 2 cases the presence of clear esophageal AC cells was histopathologically demonstrated. Correlating the forms of foveolar *pattern* with the histopathological types of MCE, we found that about 60% of patients with MCE (28 cases), who presented at the endoscopic examination a foveolar *pattern* of villous or dentate type, were patients

subsequently demonstrated histopathologically with IM (Table 6), moreover, the forms of dysplasia were also associated with various changes or vascular distortions of the stromal architecture. 39 cases of MCE (64%, t-test, p = 0.05) without dysplasia were confirmed, of which 30 cases were diagnosed with IM. MGD was attested in 16 cases, with a practically similar distribution for different histopathological forms of MCE, and AGD constituted 6.5% (4 cases) and esophageal AC 3.2% (2 cases). The most common complication, and this being probably determined by the natural course of the disease, was the association of dysplasia (Figure 10).

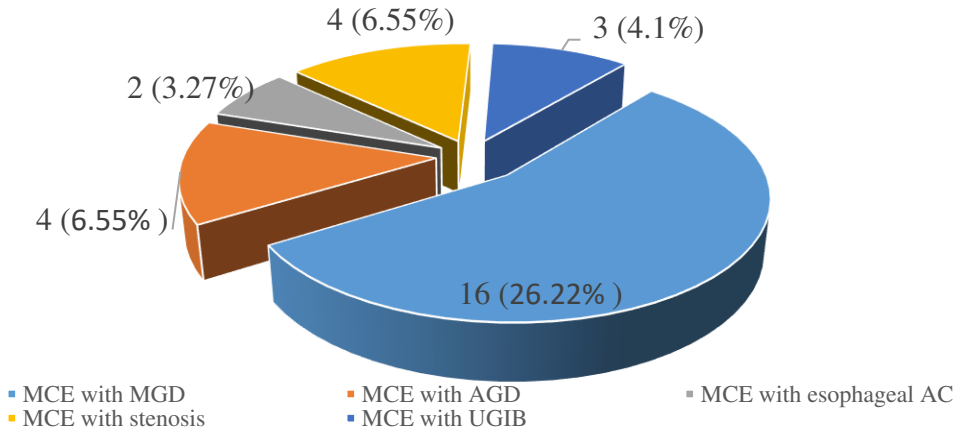


Figure 10. **Frequency of complicated MCE forms.**

Immunohistochemically, the diagnosis of MCE was confirmed by CK7, CK20, EMA cytokeratins in 100% of cases. It was found that CDX 2 characterizes specialized goblet cells and it was positively assessed in 80% of cases with IM, and 30% of cases of GM. Ki67 in IM had a more intense coloration in the glands and glandular ducts (100% cases, p = 0.001), and in the histopathological bioptates of GM they were practically absent and this correlated with the index of cell proliferation in the duct of the glands. AMACR and p53 may be biomarkers that may assist pathologists in detecting cases of dysplasia with a higher risk of progression. Other biomarkers were also suggested, such as p16, loss of heterozygosity, aneuploidy, tetraploidy, and epidermal growth factor receptor, reviewed by Varghese et al. [21], however, none of them has been validated in clinical practice. In the study, p53 tested positive in only 20% of cases of IM with a poor coloration (cases with indefinite dysplasia) and negative in the colorations for GM.

Immunohistochemistry in the MCE research groups (group I) versus AC (group II) determined: in group I its expression was attested in all patients and had an average of 60%, in group II p53 was positive only in 2 patients with IM who associated MGD and had an immunohistochemical expression of 20%. The expression of the CK7+/CK20 markers averaged 70% in research group I and 100% in research group II; CDX 2 expression characterizes goblet cells and was positively assessed in 80% of the patients in research group I and in 80% of cases with IM, and 30% of GM cases in research group II; in group II, Ki67 in IM was positive in 100% of cases and had a more intense coloration in glands and glandular ducts, and in the histopathological bioptates of GM they were practically absent, and in the research group I it was positive on average in 70% of patients with esophageal AC.

4. Medical-surgical management in columnar epithelial metaplasia of the esophageal mucosa.

The surgical treatment was applied to all the patients included in the basic group of the study, but the type of surgical interventions was different, directed both by the histopathological result of the metaplastic disease obtained preoperatively and by the extent of metaplasia in the surface of the

esophageal mucosa. The selection of the character and volume of the surgical intervention was determined by the induced complications of MCE, as well as by the associated pathology: thus, in the case of patients with IM and MGD, endoluminal treatment was certainly indicated, followed by antireflux surgery as a further step in the complete resolution of the etiopathogenetics of the disease. In the case of the association of stenoses, recurrent hemorrhages, Barrett's or Savary's ulcers, of the esophageal AC, there was a clear indication for esophagoplasty. Divergences in therapeutic approaches occurred in patients who, although they had confirmed AGD or early AC in which there were no possibilities to assess lymph node invasion, were decided to be submitted to surgical resections of the esophagus to the detriment of a mucosectomy. The medical-surgical algorithm of the patients included in the research group determines the order of the staged treatment: first endoluminal operations being performed, and subsequently laparoscopic or open antireflux surgical interventions being associated. The succession of the treatment methods was different, but, for the most part, it was started with antireflux and acid-suppressive drug treatment (for 3-6 months, divided into two stages), on the background of which the examinations were being completed for a definitive establishment of the diagnosis. The endoluminal endoscopic stage was the first stage, given that the antireflux operation anatomically modifies the EGJ, further making the manipulation more difficult to perform on the esophageal mucosa. The therapeutic medicinal arsenal for patients with MCE included in the research group varied depending on the pathology: from medicinal treatment with PPI, gastroprotectants, prokinetics in reflux esophagitis; the association of standard hemostatic medication in case of erosions and hemorrhagic ulcers; surgical interventions highly specialized in stenosis.

4.1 Endoluminal surgical treatment

Endoscopic mucosectomy (EME) involves the excision of the esophageal mucosa over the entire affected area and deep through the submucosa, with techniques of interventional endoscopy. It is important to respect the criteria of resection radicality (R0, Rx, R1) and to keep the post-resection *sample* preferably *en bloc*. The risk of lymphatic disease should be "zero" or "almost zero". The early stage of AC limited to the mucosa and superficial submucosa (<500 nm) represents this negligible lymphatic risk and can be treated endoluminally as an alternative to surgical resection.

Indications for endoluminal treatment:

- Intestinal metaplasia without dysplasia;
- Forms of MCE with MGD and AGD;
- Early AC T1m-sm1.

Contraindications for endoscopic MCE eradication therapy:

- Patients who are on medication for concomitant conditions and who at the moment are at increased risk for hemorrhage caused by EME;
- Erosive-ulcer esophagitis/other forms of esophagitis (infectious) in the acute inflammation phase;
- The presence of esophageal varices in the metaplasia area;
- Patients who cannot follow the post-ablation and post-EME treatment regimen;
- Presence of posterosive, post-ulcer strictures or scars in the metaplasia area.

Endoscopic modalities include the following techniques:

1. Endoscopic Mucosal Resection (EMR);
2. Endoscopic Mucosal Dissection (EMD);
3. Ablation techniques: electrodestruction, cryodestruction, plasma argon coagulation (APC),

photocoagulation, radioablation, etc.

In the research group EMR was used *en bloc* (4 cases) and *in fragments* (3 cases), and was dictated both by the histopathological result and by the degree of metaplasia extension into the surface, estimated according to the C&M Prague criteria. EMD was applied to patients where IM was found in association with circumscribed dysplasia. APC in the study was imposed by its high efficacy, accessibility and reduced complications, and was the most common form of endoablation. Endoscopic procedures were applied in a single interventional stage for the cases with limited circular extension (less than 1/3) and in two-three stages for forms of extended circular metaplasia (greater than 1/3), with a time distance of 1.5-2 months between the procedures. Each stage of ablation was followed by a standard hygienic-dietary regimen and medicinal therapy according to the protocol. Re-epithelialization with the formation of squamous neoepithelium was confirmed endoscopically and histopathologically in all the cases (Figure 11).

a b c

Figure 11. **Endoluminal MCE treatment by APC procedure:**
a) MCE with IM, b) intraoperative APC aspect, c) re-epithelialization with neosquamous tissue

Endoluminal resection treatment was applied to 49 patients (80.32%), in total, in the research group excision *en bloc* (11 cases, 22.44%) and in *fragments* (38 cases, 77.55%) were successful (Table 7).

Table 7. **Distribution of the forms of endoscopic resections in the study.**

Endoluminal intervention	Nr. of cases	Relative frequency (%)	P value
EMR	7	14.28%	p_value=0.05 ns Fisher
EMD	4	8.16%	
APC	37	75.51%	
Bipolar electrodestruction	1	2.04%	
Total	49	100%	

Note: EMR: Endoscopic Mucosal Resection; ESD: Endoscopic Submucosal Dissection; APC: Argon Plasma Coagulation.

4.2 Laparoscopic antireflux surgical treatment

The antireflux surgical treatment in the study was the second stage of the endoluminal surgical interventions, and as surgical indications for them served the paraclinical attestation of the LES incompetence and GERD confirmed at the pH-metric examination and high-resolution esophagomanometry. The appropriate time for the application of antireflux interventions was

estimated to be at least 4 weeks after the endoluminal intervention, a moment explained by the fact that shorter periods of time maintain a local perinflammatory process, at the EGJ level, and make it much more difficult to mobilize the EGJ and the "*abdominization of the esophagus*" in the surgical act, and, consequently, increase the duration of the surgical intervention. The type of surgical interventions was mainly dictated by the degree of functional damage to the esophagus. The Lortat-Jacob procedure in the 270° modified variant was applied in the case of the association of GERD with fragmented peristalsis and/or esophageal hypotonia (42.85%), the Nissen-Rosseti type (38.77%) was indicated in certain cases of intact esophageal peristalsis and the presence of severe reflux, the Hill-Dor procedure (18.36%) was indicated in cases of severe damage to esophageal peristalsis or in the cases where the anatomical particularities did not allow the application of a total antireflux valve (Figure 12).

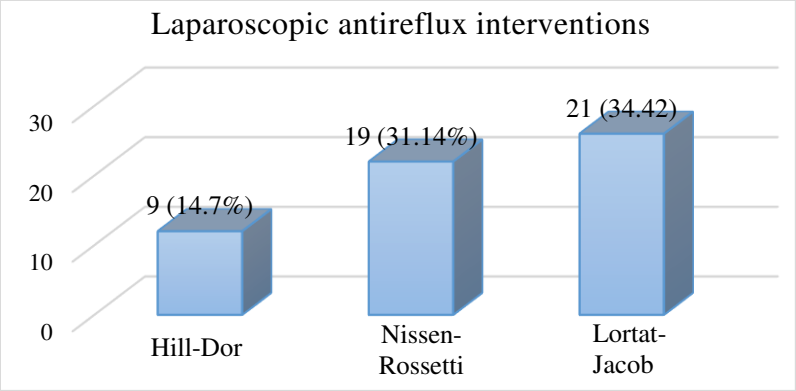


Figure 12. **Ratio of the antireflux surgical interventions in the study group**

In 43 cases (71%) posterior crurorrhaphies were applied with the fortification of the esophageal hiatus, and in 18 cases (29%), where the dimensions of the esophageal hiatus exceeded the diameter of 3 cm, it was pleaded for the combination (anterior and posterior) of crurorrhaphy in order to avoid the complications of postoperative dysphagia by *esophagus angulation*. All antireflux surgical interventions were performed laparoscopically.

4.3 Open surgical treatment of complicated epithelial metaplasia

In the study, 47.54% of patients were diagnosed with complicated forms of MCE: Barrett's ulcer with UGIB 3 cases (4.1%), post-inflammatory stenosis 4 cases (6.55%), MGD 16 cases (26.22%), AGD 4 cases (6.55%), esophageal AC 2 cases (3.27%). The diversity of the forms of MCE complications has dictated the application of different surgical treatment tactics. Thus, in the case of patients with complicated MCE (except for MGD), open surgical treatment was indicated - esophageal resections with subsequent esophagoplasties and lymphodissection as appropriate. In 50% of cases (6 patients) the stomach (Lewis procedure) was used as a substitute for the esophagus.

4.4 Results of the surgical treatment in MCE

The efficacy of the medicinal treatment in the research group was 94% (57 patients) for GER control in the first course of treatment (according to the protocol of the research project), but with the restoration of heartburn in the first week after abandoning treatment. Los Angeles esophagitis stage regression on endoscopic examination was attested in 46 patients (75.4%). In 28 patients (45.9%) stage A from B, 18 patients (29.5%) stage B from C. In the control group, after the administration of the medicinal treatment in all the patients, there was a regression of the esophagitis signs, in 3 cases (4.91%) after the endoscopic reassessment ultra-short BE (USBE)

was detected in the patients from short-segment BE (SSBE) found at the primary endoscopic examination, 1 case (1.63%) after the attenuation of the inflammatory signs in the esophageal mucosa and re-evaluation MCE was ruled out and in no case was there a decrease in MCE expression in the control histopathological bioptates. In 2 patients who did not receive conservative treatment, the length of the metaplasia segment was increased with 1.01 ± 0.3 cm (95% CI 0.83-1.21) and 2.02 ± 0.21 cm, respectively (95% CI 1.93-2.46) diffusely for a supervision of 5 years. None of the patients included in the follow-up group developed dysplasia. Postoperative complications of endoluminal surgical interventions applied in the research group are characterized according to Table 8.

Table 4.2 **Postoperative complications of endoluminal treatment in the study**

	EMR		**EMD**		**APC**	
	Immediate	*Late (>1 month)*	*Immediate*	*Late (>1 month)*	*Immediate*	*Late (>1 month)*
Hemorrhage	2	-	1	-	-	-
Retrosternal pain	1	-	1	-	2	-
Dysphagia	-	-	-	-	-	-
Esophageal stenosis	-	1	-	-	-	-
”Remaining islets” of MCE	-	-	-	-	-	1
MCE recurrence (>1 year)	-	-	-	-	-	-

For the patients in the research group who underwent endoluminal surgical interventions (49 cases) - in 100% cases neoepithelialization of the resected tissue was determined at the control EDS examination during the late supervision period and in no case was MCE recurrence determined. According to the manometry results, we found that the antireflux surgical intervention is able to control GER by strengthening the LES, but the type of the antireflux valve needs to be correlated with the preoperative manometric results. Overall, in the research group, the postoperative evolution in patients with complicated forms of MCE was different, even individualized. Thus, the patients who underwent minimally invasive surgical interventions had a favorable evolution, with very good results in the immediate and late postoperative period (with a clinical-paraclinical follow-up > 2 years), without major complications, while patients after esophagoplasty had a evolution marked both by the background pathology (patients with esophageal AC, UGIB, with concomitant pathologies), by the operating time, and by the occurred postoperative complications. The hospitalization of these patients lasted with an average of 18.3 ± 2.8 days (95% CI 16.9-20.7), postoperative complications in the immediate period were remarked by 2 (3.27%) cases of pulmonary artery thromboembolism (PATE), 4 (6.55%) cases of dehiscence of the sutures of postoperative anastomosis, and in 2 (3.27%) cases by fistulization. Postoperatively, 2 patients died, postoperative lethality constituting 3.27%. The direct cause of death was determined by the background pathology, esophageal AC, postesophagectomy conditions with dehiscence of the anastomosis sutures, complicated by mediastinal and pleuro-pulmonary septic-purulent processes. Statistical processing of the data obtained by monitoring the quality of life assessed by the *HRQL* score showed a statistically significant difference in the research group (pre- and postoperatively, p_value = 0.0000001 with the McNemar test), thus proving a good efficiency of the fundoplication for life quality control. The highest average value of the score was attested in patients in the baseline group in the preoperative period and patients in the control group - 40.1 ± 1.2 (95% CI 36.8-42.9), and the lowest one was in patients in the

baseline group after the application of the antireflux surgical treatment 2.1 ± 1.1 (95% CI 1.7-3.9). This index decreased significantly in patients following medicinal treatment, but correlated with the maintenance of the histopathological changes for MCE. We consider this a consequence of the decrease in GER and in the inflammatory lesions of the mucosa, because 43.2% (26 cases) of the patients in the control group showed an index increase at the abandonment of the medicinal treatment up to 25.3 ± 2.1 (95% CI 23.1-28.2). In the statistical processing of the quality of life data, we found significant differences in the pre- and postoperative research group (p_value = 0.006686 - Kruskal-Wallis test), between the postoperative research group and the control group (p_value = 0.000000 - Kruskal-Wallis test), which reveals that the presence of reflux (GERD) is the most acute suffering in the patient with MCE with involvement in the quality of life of the patients.

GENERAL CONCLUSIONS AND PRACTICAL RECOMMENDATIONS

GENERAL CONCLUSIONS

1. Columnar metaplasia of the epithelium of the esophageal mucosa is the result of evolution long duration of Gastro-Esophageal Reflux Disease with an average of 3,03 years according to the data the study. The most important factors with particular impact on the evolution toward esophageal metaplasia are: prolonged gastroesophageal reflux, hiatal hernia, smoking, obesity, age >50 years.
2. GERD and its forms complicated by MCE remain a current problem, determined both by an increasing incidence of the disease and by the new possibilities of endoscopic and histopatomorphological diagnosis. Advanced upper digestive endoscopy by visualizing and differentiating the cellular and vascular *pattern* allows performing the targeted biopsy of the metaplastic tissue, which consequently increases the diagnostic accuracy, as well as the procedural cost for patients at the stage of *screening* and monitoring of the disease.
3. Clinical-endoscopic supervision is required for both the patients who have undergone endoluminal surgical treatment and the patients in the control group with medicinal treatment, and the indication for metaplastic tissue ablation will be: the extension of the lesion, association of the nodular forms or dysplasia.
4. Early detection of patients with MCE is a mandatory condition for the involvement of the multimodal treatment (medicinal, endoluminal, antireflux) and increases the rate of minimally invasive interventions in this disease up to 80%.
5. *Goblet* cell formation is an evolutionary, pathogenetic stage of MCE with progression to IM, dysplasia, and subsequent development of immunohistochemically demonstrated esophageal AC. Mucin immunohistochemistry, the study of cell cycle abnormalities, as well as genetic changes can be methods of assessing and monitoring the progression of dysplasia.
6. The basic treatment for patients with MCE should remain a multimodal one, focusing on the suppression of GER (in its various forms of approach, preferably minimally invasive), obligatorily associated with endoluminal ablation techniques of the metaplastic tissue for dysplasia-associated GM and for IM with/without dysplasia.
7. Along with the implementation of multimodal surgical tactics with a well-defined trajectory, the management of MCE has changed, and this has allowed to improve the treatment results of the patients with MCE, both in the early postoperative period and in the late one, one of which is the significant increase in the quality of life in patients with minimally invasive surgical interventions compared to laborious surgical interventions, resection operations being a necessity justified only in the advanced forms of MCE (esophageal AC, stenosis, repeated UGIB from ulcers).

PRACTICAL RECOMMENDATIONS

1. The accepted and recommended risk factors for MCE for diagnostic supervision intervals and interventions are: the length of the metaplasia segment and the result of the histopathological interpretation of systematic biopsies. Other risk factors for the patients, including demographic characetristics, smoking, gender, obesity, ethnicity, age of the patients, biomarkers and endoscopic adjuvants, remain under discussion and are insistently assessed.
2. Assessment and differentiation of the forms with dysplastic potential, such as: villous/dentate *pattern* and vascular distortions, in patients with MCE are considered high risk areas and will be obligatorily subject to targeted biopsy.
3. The treatment of MCE with IM requires a multidisciplinary approach, which involves interdisciplinary cooperation (gastroenterologist, endoscopist, histopathologist and surgeon), with the timely application of the possibilities of endoluminal ablation in the first step and antireflux surgical treatment in the later stage.
4. The nature and volume of the endoluminal surgical intervention will be determined by the histopathological form of metaplasia and/or dysplasia, as well as by the degree of process extension into the surface of the esophageal mucosa.
5. The multimodal treatment of MCE associated with refractory GERD and LES incompetence obligatorily includes the endoluminal intervention in the first stage, followed at least at 2 weeks by the laparoscopic antireflux surgical intervention.
6. MCE with GM without dysplasia, which has no indications for antireflux surgical treatment, does not require endoluminal endoscopic treatment, will be monitored endoscopically according to the *guidelines* in force.
7. MCE with GM without dysplasia and with indications for antireflux surgical treatment (difficult refractory or non-refractory reflux esophagitis for medicinal treatment) will be preceded by endoscopic ablation with argon plasma in any technical variant. MCE with GM and MGD will be treated endoscopically, regardless of the surgical plans on the EGJ, by endoscopic ablation with argon plasma, preference being given to the hybrid method with submucosal pre-ablation *lifting* and double scraping of the ablated layer.
8. MCE with GM and AGD, and early neoplasms on this background will be treated in all cases by EMR or ESD (depending on the size of the lesion), obligatorily associated with the histological examination of the post-resection sample. Open interventions are reserved for the stenotic and neoplastic complications of GERD, reinterventions, but also associations with other pathologies.
9. In MCE with SS in which the longitudinal extension is more than 5 cm and the circular one - greater than 2/3 Ø caution is required, in order to avoid the risk of postoperative scar stenosis. The surgical interventions are recommended to be staged in several sessions with a difference of 3-4 weeks, time required for the re-epithelialization of the ablated tissue.
10. Patients who are going to be submitted to antireflux surgical treatment will undergo a complex functional diagnostic examination: standard manometric examination (as well as manometric MRS challenge tests) and diurnal pH-metry for a complete evaluation for the correct selection of the antireflux surgical intervention in accordance with the standards of the clinic.

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LIST OF PUBLICATIONS AND SCIENTIFIC EVENTS

where the research results the doctoral thesis in medical sciences were presented.

SCIENTIFIC WORKS

- **Articles in scientific journals abroad:**

  ✓ **Articles in ISI-Thomson end SCOPUS journals**

  1. Ungureanu S., Sipitco N., Vidiborschii V., **Fosa D.** Electrical Stimulation as an Alternative Treatment in Gastroesophageal Reflux Disease - Clinical Study. *În Chirurgia*. 2019; 114(4); 451-460.

- **Articles published in national journals:**

  ✓ **B-category published articles**

  1. Ungureanu S., Istrate V., **Fosa D**., Sipitco N. Tratamentul etapizat al bolii de reflux gastro-esofagian asociat cu esofag columnar metaplaziat. *Buletinul Academiei de ştiinţe a Moldovei.* 2017; 2 (54): 180-184.

  2. **Fosa D.** Esofagul columnar metaplaziat: actualitatea problemei. *Buletinul Academiei de ştiinţe a Moldovei. Ediţie specială aniversare la 200 de ani a IMSP SCR*. 2017; 5 (55): 164-168.

  3. Ungureanu S., Șipitco N., Lepadatu C., **Fosa D.** Tratamentul chirurgical al bolii de reflux gastroesofagian: studiu retrospectiv, pe serie de cazuri. *Revista de Ştiinţe ale Sănătăţii din Moldova*. 2017; 11(1): 69-77.

  4. **Fosa D.** Abordări inovative în tratamentul bolii de reflux gastroesofagian complicate cu esofag columnar metaplaziat. *INTELLECTUS*. 2017; 2: 95-99.

  5. **Fosa D.** Evoluția noțiunii de esofag Barrett. *Arta Medica*. 2018; 1(66): 35-38.

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- **Articles in national scientific collections:**

  1. **Fosa D**, Ungureanu S, Gladun N., Șipitco N., Istrate V. Tendințele actuale în diagnosticul și tratamentul esofagului barrett. *Analele ştiiţifice ale USMF „N.Testemiţanu”*. 2013; 4: 44-48.

  2. Șipitco N.,. Ungureanu S., Lepadatu C., **Fosa D**., Cetuleanu E. Hemoragie digestivă superioară din ulcer gastric liniar în herniile hiatale gigante: ulcer Cameron. *Culegere de articole ştiinţifice consacrată aniversării a 90-a de la naşterea ilustrului medic şi savant Nicolae Testemiţanu.* 2017; 1: 310-313.

- **Articles in international scientific collections:**

1. **Fosa D**. Innovative approaches to the treatment of gastroesophageal reflux disease complicated with metaplasia of columnar esophagus. *Catalogul oficial al Salonului Cadet INOVA'19*. 2019; 1: 89-95.

- **Articles published for scientific international conferences:**

✓ **From Republic of Moldova**

1. Ungureanu S., Șontea V., Vidiborschi V., Lepadatu C., Șipitco N., **Fosa D**. Using of ISM radio bands for wireless charging of medical implants. *International Conference on Microelectronics and Computer Science, October 19-21, 2017, Chișinău,* 2017. p. 360-363.
2. Șontea V., Ungureanu S., Șipitco N., **Fosa D.**, Vidiborschi V. Method for Performance Evaluation of Electrostimulation of the Lower Esophageal Sphincter. *4th International Conference on Nanotechnologies and Biomedical Engineering Proceedings of ICNBME-2019*, *18-19 septembrie, Chișinău,* 2019. p. 417-420. ***(SCOPUS)***.
3. Ungureanu S., Șontea V., Vidiborschi, V. Șipitco, N., **Fosa D**. Rationale of output parameters for lower esophageal sphincter stimulator. *6 th International Conference "Telecommunications, Electronics and Informatics", 24-27 mai 2018, Chișinău*, 2018. p. 392-393.
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- **Invention patents, registrations certificates, materials for inventions salon**

I. Invention patents:

1. Ungureanu S., **Fosa D**, Gladun N. Metodă de tratament al herniei hiatale gigante. Brevet de invenție MD 1034. BOPI 05/2016, G2.2016.05.03.
2. Ungureanu S., Gladun N., Șipitco N., Lepadatu C. **Fosa D**. Metodă de tratament a incompetenței sfincterului esofagian inferior. Brevet de invenție MD 1082. BOPI 08/2017, G2.2016.10.12.
3. Ungureanu S., Gladun N., **Fosa D**, Toma A., Rusu S. Metodă de tratament al diverticulului esofagian. Brevet de invenție MD 1104. BOPI 03/2018, G2.2016.06.16.

II. Innovation certificates:

1. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metoda de crurorafie combinată (anterioară și posterioară) laparoscopică în hernia hiatală. *Certificat de inovator nr. 5467*.

2. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metoda laparoscopică de crurorafie posterioară în „8" în herniile hiatale. *Certificat de inovator nr. 5470*.

3. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metoda laparoscopică de tratament a herniilor hiatale gigante cu plasă sintetică bifațată. *Certificat de inovator nr. 5468*.

4. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metoda laparoscopică de tratament a herniilor hiatale gigante cu sutură V-Lock. *Certificat de inovator nr. 5469*.

5. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metode sutură în „buclă dublă" a plilierilor diafragmali în herniile de dimensiuni mari a hiatusului esofagian. *Certificat de inovator nr. 5479*.

6. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metoda de sutură a hiatusului esofagian cu petec de proteză sintetică (polipropilen PTFE) *Certificat de inovator nr. 5480*.

7. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metoda de tratament a incompentenței sfincterului esofagian inferior prin electrostimulare. *Certificat de inovator nr. 5483*.

8. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metoda de fixare a electrozilor introperator pentru stimulare asfincterului esofagian inferior. *Certificat de inovator nr. 5484*.

9. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metodă de tratament a refluxului gastroesofagian prin aplicarea fundoplicației cu hemivalvă anterioară la 270^0. *Certificat de inovator nr. 5494*.

10. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metodă de „sutură complexă" în operația antireflux pentru BRGE. *Certificat de inovator nr. 5493*.

11. Sergiu Ungureanu, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**, Garaba Alecu. Metodă de esocardiomiotomie modificată (în unghi de 110^0, deschis în stînga). *Certificat de inovator nr. 5501*.

12. Sergiu Ungureanu, Toma Alexandru, Rusu Sergiu, **Fosa Doina**, Covila Artiom. Metodă modificată de diverticulectomie esofagiană. *Certificat de inovator nr. 5514*.

13. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metodă de electrostimulare a SEI în perioada postoperatorie prin aplicarea impulsurilor cu frecvență înaltă. *Certificat de inovator nr. 5513*.

14. Sergiu Ungureanu, Gladun Nicolae, Sipitco Natalia, Lepadatu Cornel, **Fosa Doina**. Metodă de elecție în determinarea tacticii chirurgicale a refluxului gastro-esofagian. *Certificat de inovator nr. 5512*.

15. Sergiu Ungureanu, Gladun Nicolae, Fosa Doina, Sipitco Natalia, Lepadatu Cornel. Manometria esofagiană preoperatorie o metodă de elecție în determinarea tacticii chirurgicale a refluxului gastro-esofagian. *Certificat de inovator nr. 5511.*

III. Implementing acts

The results of the study were implemented in the scientific-didactic process: Department of surgery no. 4, General Surgery section of IMSP "Timofei Moșneaga" Republican Clinical Hospital.

1. **Metoda de crurorafie combinată (anterioară și posterioară) laparoscopică în hernia hiatală.** Ungureanu Sergiu, Gladun Nicolae, Șipitco Natalia, Lepadatu Cornel, Fosa Doina. *Act de implementare nr.13 din. 03.04.2015.*
2. **Metoda laparoscopică de tratament a herniilor hiatale gigante cu plasă sintetică bifațată.** Ungureanu Sergiu, Gladun Nicolae, Șipitco Natalia, Lepadatu Cornel, Fosa Doina. *Act de implementare nr. 14 din. 03.04.2015.*

3. **Metoda laparoscopică de tratament a herniilor hiatale gigante cu sutură V-Lock.** Ungureanu Sergiu, Gladun Nicolae, Șipitco Natalia, Lepadatu Cornel, Fosa Doina. *Act de implementare nr. 15din. 03.04.2015.*

4. **Metoda de tratament a incompentenței sfincterului esofagian inferior prin electrostimulare.** Ungureanu Sergiu, Gladun Nicolae, Șipitco Natalia, Lepadatu Cornel, Fosa Doina. *Act de implementare nr.16din. 03.04.2015.*

- **Active participation with in scientific forums:**

✓ **International**

1. Ungureanu S., Gladun N., **Fosa D.**, Șipitco N., Lepadatu C., Istrate V. Corelarea endoscopico-morfologică în metaplazia epitelială columnară de mucoasă esofagiană. *Reuniunea Națională de Chirurgie cu participare Internațională,* Iași, România, 6-8 octombrie 2016.

2. Ungureanu S., Gladun N., **Fosa D**., Istrate V., Șipitco N., Lepadatu C. Morfological and endoscopic correlation in columnar epithelium metaplasia of esophageal mucosa. *I-й БУКОВИНСКИЙ ХІРУРГІЧНЫЙ ФОРУМ,* Чернивці, Украина, 28-29 вересня, 2017.

3. Șipitco N., Ungureanu S.; Gladun N., **Fosa D**. O abordare alternativă în tratamentul bolii de reflux gastroesofagian. *Congresul Național al Chirurgilor cu participare Internațională,* Iași, România, 5-7 octombrie 2017.

4. Ungureanu S., Istrate V., **Fosa D**., Șipitco N. Tratamentul chirugical miniinvaziv etapizat la pacienții cu esofag columnar metaplaziat. *Congresul Național al Chirurgilor cu participare Internațională*, Iași, România, 5-7 octombrie 2017.

5. Ungureanu S., Șipitco N., **Fosa D**. Ulcers Cameron complicated wiht superior digestive hemorrage. *Ediția XIXX-a Congresului Național de Chirurgie*, Sinaia, România, 6-8 iunie 2018.

6. Ungureanu S., Șipitco N., Istrate V., **Fosa D**. Principii de diagnostic și tratament al complicațiilor chirurgiei antireflux. *Conferința Națională de Chirurgie*, Craiova, România, 8-11 mai 2019.

7. Șipitco N., Ungureanu S., **Fosa D**. Tratamentul chirurgical al herniilor hiatale voluminoase. *Conferința Națională de Chirurgie*, Craiova, Romania, 8-11 mai 2019.

8. **Fosa D.** Lucrare invitată. Innovative approaches to the treatment of gastroesophageal reflux disease complicated with metaplasia of columnar esophagus. ***The International Student Innovation and Scientific Research Exhibition - "Cadet INOVA'19"*, Sibiu, România, 11-13 aprilie 2019.**

9. Ungureanu S., Șipitco N., Vidiborschi V., **Fosa D**. АЛЬТЕРНАТИВНЫЕ МЕТОДЫ ЛЕЧЕНИЯ ГАСТРОЕЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНИ. *II БУКОВИНСЬКИЙ ХІРУРГІЧНИЙ ФОРУМ,* Чернивці, Украина, 3-4 жовтня 2019.

10. **Fosa D**., Lucrare invitată. ***The International Student Innovation and Scientific Research Exhibition -"Cadet INOVA'19"*, Sibiu, România,** 26-28 martie 2020.

11. S. Ungureanu, O. Conțu, L. Constantinov**, Fosa D.** Operațiile bariatrice și boala de reflux gastro-esofagian. *NOBEZ – Abordul Multidisciplinar în Prevenția și Managementul Obezității*, Iași, România, 26-28 aprilie 2018.

✓ **National**

1. **Fosa D.** Actualități în diagnosticul și tratamentul metaplaziei epiteliale columnare de mucoasă esofagiană. *Conferința științifică anuală a cadrelor științifico-didactice, doctoranzilor, masteranzilor, rezidenților și studenților USMF ,,Nicolae Testemitanu",* secția nr. 4 Probleme actuale în chirurgie, subsecția 1 (diplomă gr.I), Chișinău, 18-21 octombrie 2016.

2. **Fosa D**. Tratamentul chirurgical multimodal al pacienților cu metaplazie epitelială columnară de mucoasa esofagiană. *Societatea de Chirurgie din Republica Moldova, întrunirea ordinară lunară a chirurgilor din Republica Moldova*, Chișinău, 30 noiembrie 2018.

3. Ungureanu S., Istrate V., Tîrbu V, Șipitco N., **Fosa D**. Diagnosticul contemporan al Esofagului Barrett. *Al XIII-lea Congres al Asociației Chirurgilor ,,Nicolae Anestiade" și al III–lea Congres al Societății de Endoscopie, Chirurgie miniminvazivă și Ultrasonografie ,,V.M. Guțu" din Republica Moldova*, Chișinău, 18-20 septembrie 2019.

4. Ungureanu S., Istrate V., Șipitco N., Toma A., Rusu S**., Fosa D**. Tratamentul chirurgical al Esofagului Barrett complicat. *Al XIII-lea Congres al Asociației Chirurgilor ,,Nicolae*

Anestiade" și al III–lea Congres al Societăţii de Endoscopie, Chirurgie miniminvazivă și Ultrasonografie „V.M. Guțu" din Republica Moldova, Chișinău, 18-20 septembrie 2019.

5. Ungureanu s., Istrate V., Șipitco N., **Fosa D**. Rezultatele tratamentului chirurgical multimodat la pacienții cu metapazie epitelială columnară de mucoasă esofagiană. *Congresul aniversar al 75-lea al USMF „Nicolae Testemițanu",* Chișinău, 21-23 octombrie 2020.

- **Posters presentations with in scientific forums:**

✓ **International:**

Saloanele Internationale ale Inovarii si Cercetarii Stiintifice:

- ProInvent 2017 Cluj, Ramânia,
- EuroInvent 2017 Iasi, România,
- Inventica 2017 Iasi, România,
- EuroInvent 2018 Iasi, România,
- CadetINOVA 2018 Sibiu, România,
- ISIF 2018, Istanbul, Turcia.

ADNOTARE

Fosa Doina „Tratamentul chirurgical multimodal al pacienților cu metaplazie epitelială columnară de mucoasă esofagiană”. Teză de doctor în științe medicale, Chișinău, 2022, care constă în introducere, 4 capitole, discuții și sinteza rezultatelor obținute, concluzii, recomandări, bibliografie din 225 titluri, 122 pagini conținut de bază, 28 tabele, 50 figuri. Rezultatele obținute sunt publicate în 45 lucrări științifice.

Cuvinte cheie: esofag columnar metaplaziat, boala de reflux complicată, Esofag Barrett, metaplazia Barrett, adenocarcinom esofagian, tratament chirurgical endoluminal, tratament antireflux.

Domeniul de studiu: 321.13 – chirurgie.

Scopul lucrării: Optimizarea rezultatelor tratamentului pacienților cu metaplazie columnară de epiteliu al mucoasei esofagiene prin implementarea metodelor contemporane de diagnostic și tratament chirurgical multimodal miniminvaziv al pacienţilor.

Obiectivele lucrării: Aprecierea comparativă a valorii diagnostice a datelor clinico-paraclinice în stabilirea diagnosticului de metaplaziei epitelială columnară a mucoasei esofagiene și analiza riscului de progresie neoplazică prin prisma examenului imunohistopatologic. Analiza comparativă a diferitor metode de tratament miniinvaziv (endoluminal și laparoscopic) cu elaborarea algoritmului complex de *screening*, diagnostic şi tratament al pacienților.

Noutatea și originalitatea științifică: S-a apreciat prin comparație valoarea și acuratețea diagnostică a diferitor metode de diagnostic clinico-paraclinic, s-au stabilit indicaţiile intervenţiilor chirurgicale pentru diferite forme de metaplazie, precum şi tipul necesar acestora pentru eradicarea substratului patologic. S-au analizat diferite metode de tratament chirurgical miniminvaziv și s-au apreciat rezultatele postoperatorii imediate şi la distanţă.

Problema științifică soluționată: S-a identificat algoritmul diagnostico-curativ al pacienților cu metaplazia mucoasei esofagiene și s-a optimizat tactica chirurgicală prin abordarea și implementarea tehnicilor operatorii miniminvazive (endoluminale și laparoscopice).

Semnificația teoretică: S-a analizat complex problema metaplaziei mucoasei esofagiene: etiopatogeneza, diagnostic, tratament, riscuri și complicații. S-au identificat posibilități noi de diagnostic (imagistic, funcțional și imunohistochimic) și tratament miniminvaziv.

Valoarea aplicativă a lucrării: A fost revizuit conceptul tratamentului metaplaziei esofagiene și propus un algoritm nou diagnostico-curativ.

Implementarea rezultatelor științifice: Rezultatele științifice, principiile fundamentale și recomandările practice sunt utilizate în procesul didactic al Catedrei de chirurgie nr. 4 USMF „Nicolae Testemițanu”, secțiile de profil chirurgical al IMSP Spitalul Clinic Republican „Timofei Moșneaga”.

АННОТАЦИЯ

Фоса Дойна «Мультимодальное хирургическое лечение пациентов со столбчатой эпителиальной метаплазией слизистой оболочки пищевода». Докторская диссертация по медицинским наукам, Кишинев, 2021 г., состоящая из введения, 4 глав, обсуждения и синтеза полученных результатов, выводов, рекомендаций, библиографии из 225 наименований, 120 страниц основного содержания, 28 таблиц, 50 рисунков. Полученные результаты опубликованы в 39 научных работах.

Ключевые слова: метапластический столбчатый пищевод, осложненная рефлюксная болезнь, пищевод Барретта, аденокарцинома пищевода, антирефлюксная терапия.

Область исследования: 321.13 - хирургия.

Цель работы: Оптимизация результатов лечения пациентов со столбчатой эпителиальной метаплазией слизистой оболочки пищевода путем внедрения современных методов диагностики и малоинвазивного мультимодального хирургического лечения.

Задачи работы: Сравнительная оценка диагностической ценности клинико-параклинических данных при установлении диагноза столбчатой эпителиальной метаплазии слизистой оболочки пищевода и анализ риска прогрессирования новообразования с помощью иммуногистопатологического исследования. Сравнительный анализ различных методов малоинвазивного лечения с разработкой комплексного алгоритма скрининга, диагностики и лечения этих пациентов.

Научная новизна и оригинальность: Диагностическая ценность и точность различных клинико-параклинических методов диагностики оценены путем сравнения, установлены показания к хирургическим вмешательствам при разных формах метаплазии. Были проанализированы различные методы малоинвазивного хирургического лечения и были оценены ближайшие и отдаленные послеоперационные результаты.

Решенная научная задача: Определен лечебно-диагностический алгоритм пациентов с метаплазией слизистой оболочки пищевода и оптимизирована хирургическая тактика за счет подхода и внедрения малоинвазивных хирургических техник.

Теоретическая значимость: Проблема метаплазии слизистой оболочки пищевода была комплексно проанализирована: этиопатогенез, риски и осложнения.

Практическое значение работы: Была пересмотрена концепция лечения метаплазии пищевода и был предложен новый лечебно-диагностический алгоритм.

Внедрение научных результатов: Научные результаты, фундаментальные принципы и практические рекомендации используются в дидактическом процессе в Отделении Хирургии №4 ГУМФ им. Николае Тестемицану, в хирургических профильных отделениях ПМСУ Республиканской Клинической Больницы «Тимофей Мошняга».

ANNOTATION

Fosa Doina "Multimodal surgical treatment of patients with columnar epithelial metaplasia of the esophageal mucosa". Doctoral thesis in medical sciences, Chisinau, 2021, consisting in Introduction, 4 chapters, discussions and synthesis of the obtained results, conclusions, recommendations, bibliography of 225 titles, 120 pages of basic content, 28 tables, 50 figures. The obtained results are published in 39 scientific works.

Keywords: metaplastic columnar esophagus, complicated reflux disease, Barrett's esophagus, Barrett's metaplasia, esophageal adenocarcinoma, endoluminal surgical treatment.

Field of study: 321.13 - surgery.

Purpose of the work: Optimizing the treatment results of patients with columnar epithelial metaplasia of the esophageal mucosa by implementing contemporary methods of diagnosis and minimally invasive multimodal surgical treatment in patients with this pathology.

Objectives of the work: Comparative assessment of the diagnostic value of the clinical-paraclinical data in establishing the diagnosis of columnar epithelial metaplasia of the esophageal mucosa and analysis of the neoplastic progression risk by the means of immunohistopathological examination. Comparative analysis of different methods of minimally invasive treatment (endoluminal and laparoscopic) with the development of the complex algorithm for screening, diagnosis and treatment of these patients.

Scientific novelty and originality: The diagnostic value and accuracy of different clinical-paraclinical diagnostic methods were assessed by comparison, the indications of the surgical interventions for different forms of metaplasia were established, as well as their type necessary for the eradication of the pathological substrate. Various methods of minimally invasive surgical treatment were analyzed and immediate and distant postoperative results were assessed.

Scientific problem solved: The diagnostic-curative algorithm of patients with esophageal mucosa metaplasia was identified and surgical tactics was optimized by approaching and implementing minimally invasive surgical techniques (endoluminal and laparoscopic).

Theoretical significance: The problem of esophageal mucosal metaplasia was complexly analyzed: etiopathogenesis, risks and complications. New diagnostic possibilities (imaging, functional and immunohistochemical) and minimally invasive treatment were identified.

The applicative value of the work: The concept of treatment of esophageal metaplasia was revised and a new diagnostic-curative algorithm was proposed.

Implementation of the scientific results: The scientific results, fundamental principles and practical recommendations are used in the didactic process in the Department of Surgery nr. 4 of the SUMP "Nicolae Testemitanu", surgical profile departments of the PMSI Republican Clinical Hospital "Timofei Mosneaga".

FOSA Doina

MULTIMODAL SURGICAL TREATMENT OF PATIENTS WITH COLUMNAR EPITHELIAL METAPLASIA OF THE ESOPHAGEAL MUCOSA

321.13 – SURGERY

Summary of the doctoral thesis in medical sciences

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