

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA**  
**DOCTORAL SCHOOL**

**PhD THESIS SUMMARY**

***STUDY REGARDING THE EFFICIENCY OF  
ENDOSCOPIC SCREENING OF BARRETT  
ESOPHAGUS***

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## **Cuvinte cheie**

**WLE – White Light Endoscopy – Endoscopie în lumină albă**

**NBI – Narrow Band Endoscopy – Endoscopie în bandă îngustă**

**AFI – Autofluorescence imaging – Endoscopie în autofluorescență**

**EB – Esofag Barrett**

**Screenig**

**BRGE – Boală de reflux gastroesofagian**

**TME – Trimodal imaging – Endoscopie trimodală**

**Adenocarcinom esofagian**

**Metaplazie esofagiană**

**Displazie esofagiană**

## PREMISES

Adenocarcinoma associated with Barrett's esophagus is the fastest growing cancer worldwide. The incidence of esophageal adenocarcinoma has increased rapidly over the last two decades, with a growth rate of 350% in males and whites between 1974 and 1994. The current increase rate in the incidence of esophageal adenocarcinoma exceeds that of any other cancers, including melanoma, lymphoma and small cell lung cancer. Today it is the third digestive cancer in frequency and one of the top ten causes of cancer in the world. During the same period, the incidence of squamous cell carcinoma of the esophagus decreased. Although 30 years ago the esophageal adenocarcinoma had low malignancy, currently over 5,000 new cases are found only in the UK. The reason for this rapid change in the epidemiology of esophageal cancer in Romania is still unknown.

The diagnosis of esophageal adenocarcinoma describes a poor prognosis, but closely related to the tumor stage. Identification of the cancer in an early stage enables a rate of 83-90% for the 5 years survival, while its diagnosis in a late stage allows only 10-15% for the 5 years survival. Barrett's esophagus is present as premalignant lesions in most cases of esophageal adenocarcinoma. Prospective studies carried out during 1990-1995 showed an increased incidence of esophageal adenocarcinoma in patients with Barrett's esophagus.

Barrett metaplasia is an acquired condition, the most common cause of which is gastroesophageal reflux. Barrett's esophagus was encountered in 10-15% of patients referred for gastro-oesophageal reflux disease. Thus, gastroesophageal reflux disease is a risk factor for esophageal adenocarcinoma. The duration and intensity of reflux symptoms are directly proportional to the occurrence of Barrett's esophagus and adenocarcinoma.

Given the lack of data on the natural history of Barrett's esophagus, on the rates of progression to cancer, on the risk factors involved in the pathogenesis and malignant transformation, there is no consensus among gastroenterologists on the time of initiating the screening, on the optimal surveillance intervals along the diagnosis of Barrett metaplasia has been established, and also on the on management of dysplasia.

## MATERIAL AND METHOD

Our study was conducted at the University of Medicine and Pharmacy of Craiova, Department of Gastroenterology and Research Center for Gastroenterology and Hepatology of Craiova between November 2007 and June 2011. We conducted a prospective longitudinal observational study, on 118 patients with typical symptoms of reflux esophagitis eligible to perform upper GI endoscopy necessary for the early diagnosis of Barrett's esophagus.

The study included two groups of patients, a main lot for which we tested the ability of different imaging techniques (white light endoscopy, autofluorescence and narrow band endoscopy) to identify premalignant epithelial lesions. The second group, a subset of the first, included patients with a diagnosis confirmed by histopathology. It served to identify the capacity of narrow band light endoscopy to characterize the previously identified lesions.

The patient selection criteria were practically the Barrett esophagus screening criteria recommended by the American Society of Gastroenterological Endoscopy. Although there is no generally valid consensus accepted for screening patients, endoscopy is recommended to be performed on male patients aged over 50, with frequent esophageal reflux episodes (several times a week), nocturnal episodes and chronic esophageal reflux disease, lasting for more than 5 years. Based on these recommendations we decided to include in the study patients aged over 50 with gastroesophageal reflux episodes with a length of more than 6 months, frequent episodes, more than 3 / week and patients with nocturnal episodes.

Biopsy was performed during classic digestive endoscopy examination according to the Seattle protocol and during narrowband and autofluorescence examination in areas labeled as suspicious. To compare the accuracy of the white light endoscopy with random sampling biopsies and the NBI and AFI technique, targeted biopsies were performed, from suspicious regions and also randomly, from 2 to 2 cm in four quadrants, in patients that did not present dysplasia, respectively from 1 to 1 cm in patients who were identified with dysplastic areas. All biopsies were taken using a standard biopsy forceps and then placed in containers that contained a 10% formalin solution.

The subgroup consisted of 46 patients with histopathologically confirmed Barrett's esophagus, subpopulation of the main lot. The purpose of the examination was to compare the accuracy of modern imaging techniques such as NBI in assessing previously identified lesions. As in the case of the main group, the histopathological examination of the biopsy piece was the standard against which results were compared.

## RESULTS AND CONCLUSIONS

The average age of patients was 56 years (54,9757- 58.0000, 95% CI, P <0.0001). Most patients were aged between 50-59 (55 representatives), followed by the range 60-69 years (37 representatives). In terms of gender distribution, the overwhelming majority was represented by males, for whom the frequency is more than 2 times higher than in women (82 patients vs. 36).

The patients were examined by classic, white light endoscopy and through the AFI and NBI technique. Biopsy fragments were obtained and were used to establish the diagnosis. After examining the lot was found no injuries in a number of 15 patients, reflux esophagitis lesions in a number of 53 patients, stenosis or esophageal ulcers in 2 patients. Barrett's esophagus was identified in a number of 46 patients, their share in the study group being of 44.92%. We identified esophageal cancer in 2 patients.

The registered symptomatology had a broad spectrum, from chest pain to swallowing, heartburn, acid regurgitation and vomiting. Although no symptoms stood out clearly, heartburn and acid regurgitation symptoms were most frequently mentioned. Statistically, heartburn was present in most patients (n = 91.36%), followed by acid regurgitation (n = 78.2%). The frequency of symptomatic episodes correlates with the degree of esophageal lesions progress. The presence of symptoms at least once a week was associated with an odds ratio of 3.9900 (1.5307 to 10.4005) for the occurrence of EB. For patients who accuses two or more symptomatic episodes per week we notice an increase in the probability of the presence of EB (OR = 5.6000 (1,7008 - 18,438) ). By comparing the likelihood of EB lesions with the ER, we note that if for patients with not more than one episode per week the risk is similar in both groups following that in those with more frequent symptomatology (more than 2 times / week) the risk for the first category increases. Symptom score was similar in patients with ER and those with of EB, with an average value for the first category and the second.

The subgroup of patients with Barrett's esophagus was composed of patients who had confirmed lesions, comprising a number of 46 representatives. The average age was 63 years, with the lowest value 43, and the highest value 69 years. Most were aged between 61-70 years (25 patients), followed by the range 51-60 years (18 patients). EB lesions were found particularly in males, with a male / female ratio of approximately 2:1 (69,07 vs. 30,43).

Of all patients identified with EB, EBSL was identified in 21 patients and EBSS in 25 patients. Most patients presented EBSS, their frequency being of 54% compared to only 46% for EBSL.

Most patients who had Barrett's esophagus lesions were overweight patients. A total of 40 patients, accounting for 87% of the total lot with Barrett's esophagus, had a BMI of more than 30.

A significant percentage had hiatal hernia. Of all patients confirmed as having EB lesions, 62% were identified with hiatal hernia.

Identifying the presence of *Helicobacter pylori* showed a lower presence in patients with EB.

Upper gastrointestinal endoscopy is the most widely used and controversial method, in conjunction with the histological examination of the biopsy piece, for Barrett's esophagus diagnosis. It directs the examiner to areas requiring biopsy. Together with the histological examination of the biopsy fragment, it is the golden method for diagnosing Barrett's esophagus. Gastroenterology guidelines recommended endoscopy and histological examination of the biopsy fragment taken directly from visible lesions or through random biopsies in four cardinal points at every 2 cm. of the Barrett segment according to the Seattle protocol.

## WHITE LIGHT ENDOSCOPY

In the case of conventional upper gastrointestinal endoscopy, the per lesion analysis showed a sensitivity and specificity of 45.06% (40.48% - 49.71%) and 54.86% (51.06% - 58.62%). The calculated positive predictive value and negative predictive value had a value of 40.31% (36.06% - 44.66%) and 59.62% (55.69% - 63.47%). The per patient analysis showed a positive predictive value of 60.78% (46.11% - 74.15%) and a negative predictive value of 77.61% (65.77% - 86.89%). The classical upper endoscopy had a sensitivity of 67.39% (51.98% - 80.46%) and specificity of 72,22% (60.41% - 82.13%). The major limitation of this examination method of is primarily the poor accuracy in identifying early stages, and the lack of a grading system for endoscopically identified visual changes.

## AUTOFLUORESCENCE IMAGING

Autofluorescence endoscopy is based on the detection of natural tissue autofluorescence emitted by endogenous molecules called fluorophores. Fluorophores include collagen fibers, flavin and porphyrins. A short wavelength light beam causes the excitation of fluorophores emitting a wide range light wave. Fluorescence varies depending on the concentration and spatial distribution of fluorophores, on the metabolic status. Autofluorescence endoscopy is now used to identify both Barrett's esophagus lesions as well as esophageal adenocarcinoma and premalignant lesions. The per lesion analysis showed therefore a positive predictive value of 59.13% (54.69% - 63.45%), a negative predictive value of 94.03% (90.83% - 96.36%), respectively a sensitivity of 94.01% (90.80% - 96.35%) and specificity of 59.21% (54.78% - 63.53%). The statistical calculation indicates, the per patient analysis, a sensitivity of 95.65% (85.16% - 99.47%) and a specificity of 59.72% (47.50% - 71.12%). The positive predictive value, respectively the negative predictive one was of 60.27% (48.14% - 71.55%) and 95.56% (84.85% - 99.46%). Autofluorescence endoscopy proved to be a very sensitive method for detecting the Barrett lesions (95.70%), detecting about 29% more lesions than the classical white light endoscopy. The main disadvantage of autofluorescence examination is the low specificity and consecutively a decreased positive predictive value due to the large number of false positives, which is why this exploratory method has a limited value for clinical practice.

## NARROW BAND ENDOSCOPY

Narrow band endoscopy is a recently put into practice technique that combines high resolution endoscopy with contrast techniques without using contrast agents. It was described for the first time in 2004(57). NBI is based on the principle that different wavelengths light has different degrees of mucosa permeability. Short wavelength blue light penetrates only the surface layers, while greater wavelength penetrates deeper layers.

The first aspect followed by us was the ability of NBI endoscopy to identify Barrett's esophagus lesions. The per lesion analysis showed a sensitivity of 58.68% (53.04% - 64.15%) and a specificity of 94.65% (92.32% - 96.45%). The positive predictive value and negative

predictive values ranged at 87.32% (82.10% - 91.48%) and respectively 78.49% (75.01% - 81.69%). The per patient analysis, taking into account the most advanced lesion identified in each patient, showed values of 86.96% (73.74% - 95.06%) for sensitivity, of 98.59% (92.40% - 99.96%) for specificity, with a positive predictive value of 97.56% (87.14% - 99.94%) and a negative one of 92.11% (83.60% - 97.05%). We obtained a positive predictive value superior to the autofluorescence endoscopy, but with a lower negative predictive value. Thus, although specificity is high, the sensitivity is lower in the case of NBI endoscopy as against AFI examination.

The main benefit of narrow band magnification exploring is the good view of the mucosal and vascular pattern. The value of this method is reduced if we refer only to the ability to identify suspicious lesions. Instead, if we refer to the ability to identify lesions, its value increases exponentially.

Of the 46 patients previously diagnosed with Barrett's esophagus, the NBI examination could not be conducted for 2 patients. The per patient analysis of vascular pattern identified the presence of columnar epithelium in a number of 10 patients (22.7%), intestinal metaplasia in 23 patients (52.3%), early and high-grade dysplasia in a number of 8 (18.2%) and 3 (6.8%) patients. Following the narrow-band examination, we identified honeycomb changes in 6 patients (13.6%), cluster in 18 patients (40.9%), coiled in 13 patients (29.5%), DNA-like and irregular in 6 (13.6%) and respectively in 1 patient (2.3%). We can thus observe that most studied patients showed a cluster type aspect followed by the spiral type. There was a correlation between the appearance of the vascular structure described in the NBI examination and the evolutionary stage of the disease. Although there is no exact correlation between the histological type and the vascular aspect, the conclusion drawn is that the advanced stages of Barrett's esophagus, the dysplastic stages, may be suggested by the irregular vasculature. In addition, even the initial stages can be easily identified based on the appearance of the vascular pattern.

After the mucosal pattern analysis we found that most patients had a cerebriform-type appearance - 12 patients (27.3%), followed by long straight and villous type with 8 patients for each (each with 25%). The remaining patients had an irregular aspect type, 7 patients (15.9%) respectively round-oval, 3 patients (6.8%). Early dysplasia presented a cerebriform-type pattern in 4 cases, followed by the irregular one in 3 cases and the villous one with 1 representative. We note in this case that as the pattern layout lesions are progressing, there is an increased frequency of cerebriform or irregular aspect. Patients with high-grade dysplasia showed an irregular or cerebriform pattern type.

### TRIMODAL IMAGING

The tri-modal exploration is the most modern investigative technique for premalignant lesions in the upper digestive tract. The need to introduce it resulted from the fact that, until now, there is no complete investigation method, showing both a high

sensitivity and specificity. This method consists of a combination of the three methods, classic light endoscopy, autofluorescence and narrowband, showing the highest sensitivity and specificity levels. For this purpose we use the classical upper digestive endoscopy and autofluorescence to identify "*red flag*" areas, and narrow-band magnification to characterize the identified lesions, taking advantage of the high specificity of the latter. The exploration sensitivity and specificity values were 95.65% (85.16% - 99.47%) respectively 98.59% (92.40% - 99.96%). The positive predictive value was of 97.78% (88.23% - 99.94%), and the negative one of 97.22% (90.32% - 99.66%). We note, therefore, that the tri-modal exploration combines the advantages of each exploring technique. It has a high sensitivity, thanks to autofluorescence endoscopy, which has a high capacity for detecting the suspicious "*red flag*" areas, and a high specificity due to the narrow band, a method with a high discriminatory power.