

## ORIGINAL PAPER

# Videocapsule endoscopy and single balloon enteroscopy: novel diagnostic techniques in small bowel pathology

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### Abstract

Videocapsule endoscopic (VCE) exploration represents a major breakthrough in non-invasive imagistic, especially of the small bowel. Our study group consisted of 29 initial subjects admitted in the 1<sup>st</sup> Internal Medicine and Gastroenterology Clinic at the Emergency County Hospital of Craiova between June 2008 and March 2009. We have excluded a number of eight subjects from the VCE-group, as their pathology represented an absolute contraindication for capsule ingestion. The remaining 21 patients (11 men – 52.38% vs. 10 women – 47.61%) underwent videocapsule diagnostic investigation followed by single balloon enteroscopy with biopsy or surgical removal, where case. Large resection cups were histologically prepared in the Pathology Department of the Emergency County Hospital of Craiova. We performed a statistical analysis of the data using Fisher's Exact Test, which is applicable to small numbered lots. In five cases (23.80%) VCE investigation did not reveal any abnormalities. Five (23.80%) cases had non-tumoral pathology, all of them being inflammatory lesions. We found tumoral lesions in 11 (52.38%) cases: five (23.80%) benign and six (28.57%) malign. We found that inflammatory lesions predominantly affected subjects in the 15–30 and 30–45 years intervals ( $p=0.00103$ ), whereas tumoral lesions are positively correlated with old age, predominantly affecting the 45–60 and above 60-year-old groups ( $p=0.00216$ ). VCE combined with SBE open new frontiers for small bowel exploration. Histology remains the single most accurate test for establishing the nature of a lesion.

**Keywords:** videocapsule endoscopy, single balloon enteroscopy, small bowel, histological diagnosis.

### Introduction

Current technological progress made way for new non-invasive exploratory techniques for the digestive tract, which can be combined with revolutionary fast and safe sampling and therapeutic methods.

Videocapsule endoscopic (VCE) exploration represents a major breakthrough in non-invasive imagistic, especially of the small bowel [1]. It was developed in order to allow diagnostic evaluation of any segment of the digestive tract, from the esophagus to the colon, currently being used mainly for exploring the small bowel, where it can accurately identify lesions otherwise undetectable by conventional means.

The numbers for potential applications of this method are rising constantly. It can be used successfully in diagnosing obscure gastrointestinal bleedings [2–5], Crohn's disease [6, 7], complications of celiac disease [8, 9], intestinal lesions [10] or tumoral pathology [11, 12].

Single balloon enteroscopy (SBE), otherwise known as “push-and-pull enteroscopy” was first designed in 1997 [13]. In 2001, Japanese researchers developed the first dedicated endoscopic system.

This technique allows direct examination of the small bowel. It can be used to acquire tissue samples or in order to apply hemostatic treatment, where case. It can be performed by a single endoscopist, as opposed

to double-balloon enteroscopy where a minimum of two is required. Standard sedation may be used. It can be performed both via oral or anal route, depending on the location of the lesions, as presented by other non-invasive techniques such as VCE.

### Patients and Methods

Our study group consisted of 29 initial subjects admitted in the 1<sup>st</sup> Internal Medicine and Gastroenterology Clinic at the Emergency County Hospital of Craiova between June 2008 and March 2009.

Our entire subject lot undergone extensive endoscopic and serologic testing, all inconclusive for their respective pathology, prior to capsule ingestion.

All their pathologies represented clear indications, in concordance with current guidelines, for VCE investigation: Crohn's disease, suspicion of intestinal polyp, suspected tumoral pathology [2–12, 14].

We have excluded a number of eight subjects from the VCE-group, as their pathology represented an absolute contraindication for capsule ingestion [14]: five subjects suffered from intestinal occlusion due to chronic enteromesenteric ischemia; three subjects had intestinal occlusion by invagination/volvulus.

The remaining 21 patients (11 men – 52.38% vs. 10 women – 47.61%) underwent videocapsule diagnostic

investigation followed by single balloon enteroscopy with biopsy or surgical removal, where case.

The video capsule endoscope is an 11/26 mm swallowable device, weighting 3.7 g. It is capable of wirelessly transmitting two images per second (over 50 000 images in a usual eight-hour recording), the image field of view being 140 degrees, with a 1:8 magnification rate and 1 to 30 mm depth of field. It has a minimum size of detection of near 0.1 mm. Its main components are an optic dome, a lens system, six LEDs (light emitting diodes), the CMOS (complementary metal oxide silicone) camera module, a specially designed ASIC (application specific integrated circuit) and an antenna that helps transmitting the images to electrodes attached to the body, while allowing storage on a small portable recording device [15, 16].

We did not routinely use bowel preparation with prokinetics, as recent data [17] suggested such techniques are not always necessary. We encountered no incomplete passage incidents. Patients fasted for at least 12 hours prior to capsule ingestion. Approximately 2 liters of a polyethylene glycol solution was administered 12 to 16 hours prior to capsule ingestion. They were allowed to drink clear liquid 2 hours after the start of the procedure, light meals being permitted at a 5 hours interval. Patients were surveyed for 8 hours on site.

When performing SBE, the scope was inserted deep inside the tract of the small intestine by inflating the balloon on the distal end of the splinting tube, thus grasping the intestine. Both the scope and the splinting tube were retracted to shorten the intestine. Afterwards, the scope was again inserted from the current position. This way it could reach deep into the small intestine. The preparation for the antegrade approach required fasting, just as for normal upper gastrointestinal endoscopy. When the colonic route was chosen due to the location of the lesions, bowel irrigation using polyethylene glycol solutions was necessary. The technique followed all current protocols for SBE [18, 19].

All study material was prepared in the Pathology Department of the Emergency County Hospital of Craiova. We used tamponed a 10% formalin solution for sample-fixation. We included them in paraffin blocks, which were sectioned under the microtome, resulting five sections from three different levels, each of 3- $\mu$ m thick. Staining the samples involved usual staining, Hematoxylin–Eosin (HE).

## Results

The initial study group comprised 29 patients. Inclusion criteria were the presence of small bowel pathology inaccessible to non-surgical investigation techniques. Exclusion criteria were absolute VCE contraindications. We have reduced the group to 21 patients, which underwent diagnostic procedures. The group structure was as follows: 11 men – 52.38% vs. 10 women – 47.61%. Minimum age was 15 years, maximum age was 79 years (mean 50.28 years; standard deviation 17.48, CI 95% 6.30).

In five cases (23.80%) VCE investigation did not

reveal any abnormalities. Later SBE investigation also proved negative.

Five (23.80%) cases had non-tumoral pathology, all of them being inflammatory lesions. Patients presented with abdominal pain, accompanied by diarrhea, inappetence, vomiting, and weight loss. On the video recorded by VCE, we could observe diffuse ulcerations at mucosal level, with variable diameters, up to 1.5 cm, oriented in the long axis along the intestinal tract wall. The macroscopic aspect revealed by VCE suggested the presence of Crohn's disease.

During the histological study, we noticed that the mucosa was ulcerated, which comprised the submucosa, the muscular tunic and the serosa. In the wall thickness we could observe the inflammatory polymorphonuclear (PMN) infiltrate, with the presence of microabscesses and ulcerations resulted after evacuation of the necrosis material (Figure 1).

Two cases presented the chronic phase, characterized by the presence of a tuberculoid granuloma of inflammatory nature. The granuloma was found in the whole thickness of the wall, de-organizing the intestinal structure (Figure 2).

Tumoral lesions were found in 11 (52.38%) cases: five (23.80%) benign and six (28.57%) malign.

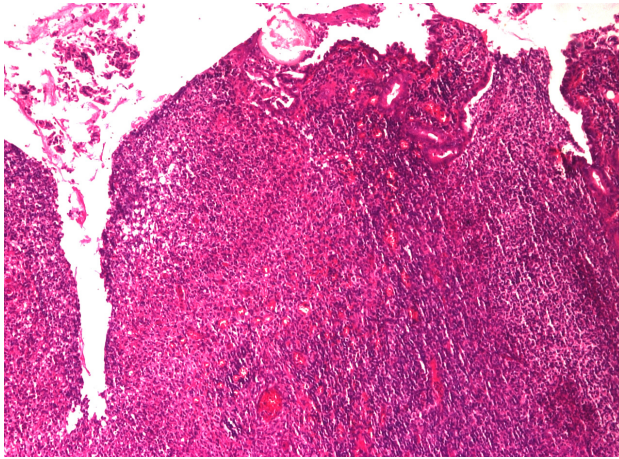
Polyps in three cases and stromal benign tumors in two represented the benign tumors we encountered. Malign tumors were represented by two cases of stromal malign tumors, two cases of adenocarcinoma, neuro-endocrine carcinoma in one case and one case of duodenal papilla carcinoma. Intestinal polyps presented as benign epithelial tumors that were identified in two men, 50 and respectively 66-year-old and one woman, 57-year-old. Patients experienced short outbreaks of abdominal pain, accompanied by inappetence and vomiting.

The aspect recorded by VCE was of an excrescence in the intestinal lumen, with variable sizes, between 0.6 and 1 cm in length and diameters between 0.4 and 0.6 cm, with smooth surface, paler than surrounding normal mucosa. Enteroscopic aspect was that of sessile polyps (Figure 3).

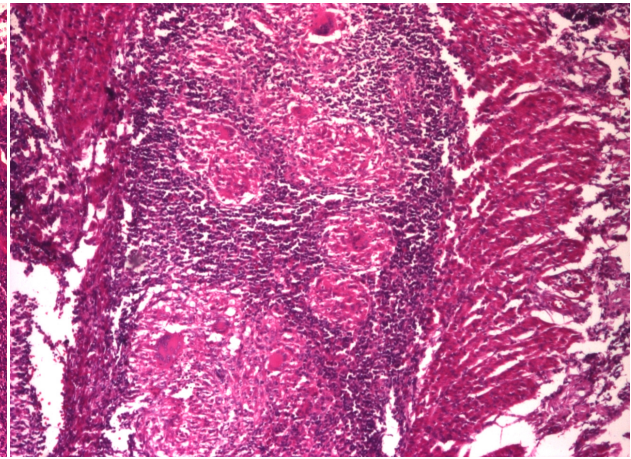
After enteroscopic polypectomy, the microscopic study revealed an aspect of tubular adenoma, composed of a conjunctive-vascular axis, with single-level intestinal cylindrical epithelium, that formed forked glands (Figure 4).

Three of the four gastrointestinal stromal tumor (GIST) cases were identified on the VCE-recording due to their ulceration. Patients presented with signs of obscure gastrointestinal bleeding, moderate anemia, accompanied by sharp abdominal pain, especially after food ingestion. The tumoral masses were identified by VCE as unique, circumscribed tumors, oval or lobular in shape, with a recognizable lift of the mucosa.

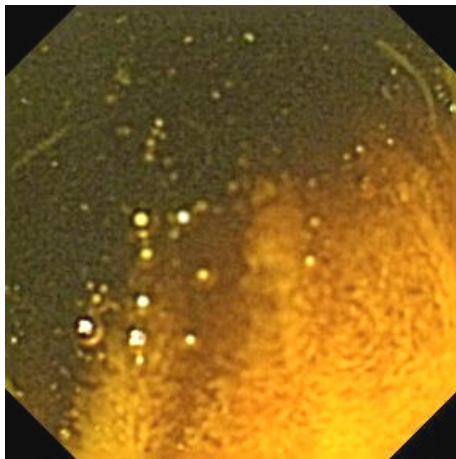
Surgical resection was needed in all four cases. Malignancy was determined on histological features. The section has a plane, granular surface, with blood vessels, collagenized areas, lysis and hemorrhage. Degenerative alterations with the formation of cystic and hemorrhagic areas were characteristic for large malignant stromal tumors.



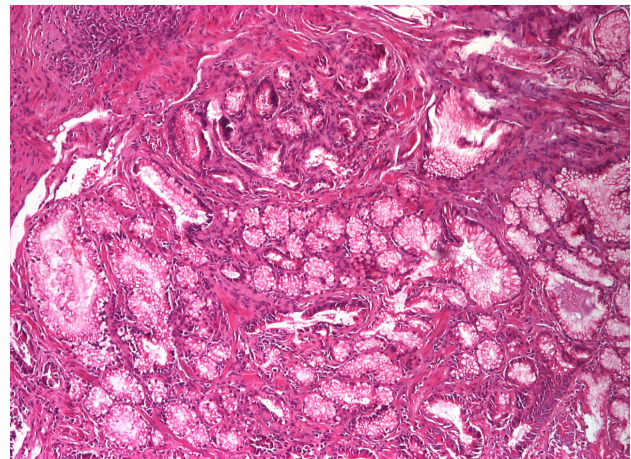
**Figure 1 – Crohn's disease: profound wall ulceration, comprising the mucosa and submucosa, abundant subadjacent inflammatory infiltrate with the formation of microabscesses (HE stain, ob.  $\times 40$ ).**



**Figure 2 – Crohn's disease: inflammatory granulomas in the muscular tunic (HE stain, ob.  $\times 40$ ).**



**Figure 3 – Capsule endoscopy: image of an intestinal polyp, distal jejunum.**



**Figure 4 – Adenomatous tubular polyp: vascular axis and ramified glands, some dilated, separated by discrete stroma (HE stain, ob.  $\times 40$ ).**

When histologically analyzed, the peripheral level of the tumor showed a hypertrophied and hyalinized muscular tunic. In two cases, the muscular fibers partially surrounded the tumor, like a capsule, and were mixed with the muscular fibers of the mucosa. The muscular fascicles entered the tumor, forming septae that delimited lobules from the tumoral cells, also ulcerating the mucosa (Figure 5).

The benign tumors were myxoid stromal tumors (one case) and with neural differentiation (in another case). The myxoid stromal ones were composed of round/elongated cells, arranged in fascicles and spirals, with oval nuclei, without atypical mitosis and with myxoid abundant stroma (Figure 6). The one with neural differentiation was composed by elongated cells, arranged in fascicles and spirals, with oval nuclei (Figure 7).

We did not find a perfect delimitation between the smooth muscular tissue and the tumoral cells, more like a merge between the two types of cells at the periphery of the tumor (Figure 8).

Two out of four cases of stromal tumors presented in our study were GIST tumors with a high-risk of metastasis. The malignancy criteria were: the

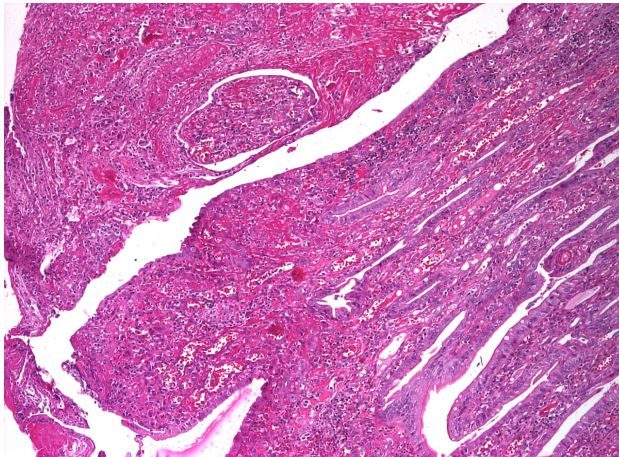
dimensions of the tumors, the neural differentiation, present in some areas, and the PCNA-index, being over 10%.

Adenocarcinoma was identified in a male patient, 57-year-old, who presented diffuse abdominal pain, moderate anemia and general discomfort. Videocapsule revealed a tumoral irregular, prominent in the small bowel lumen, aspects that we considered as suggestive for adenocarcinoma. After surgical resection, the tumor was found to be vegetant, ulcerated and infiltrative, white-yellow in color, friable in vegetant areas and with stiff walls.

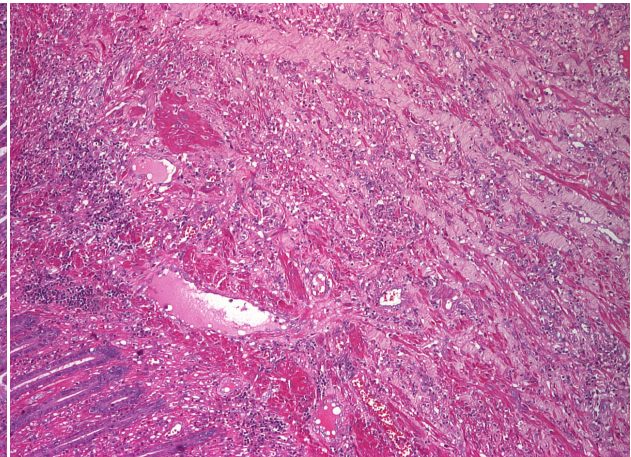
Under the microscope, it had the aspect of a moderate differentiated adenocarcinoma. The tumoral cells were arranged in glanduliform structures of various shapes and sizes, with cylindrical neoplastic epitheliums, with a leveled arrangement and intra-luminal papillary structure formation (Figure 9). The adenocarcinoma was ulcerated (Figure 10) and totally infiltrated the intestinal wall.

Neuroendocrine carcinoma was encountered in our study in a 61-year-old woman. She presented with pain in the lower left abdominal quadrate, accompanied by inappetence and vomiting.

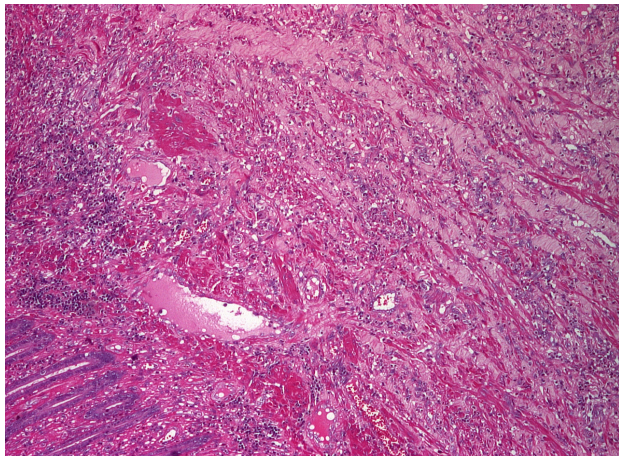




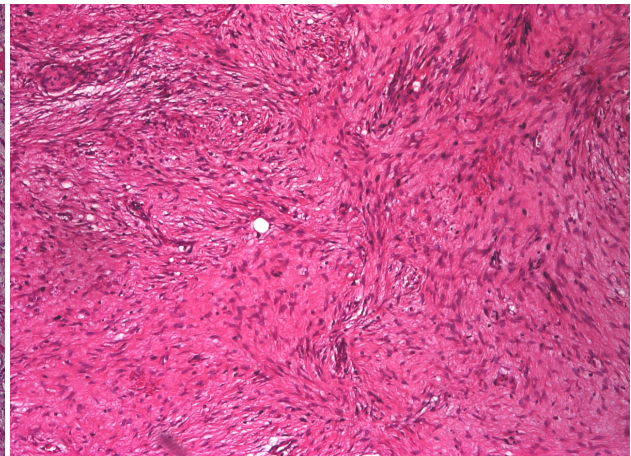
**Figure 5 – Stromal tumor with low metastatic risk: smooth muscle fiber fascias, which surround lobules of tumoral cells and ulcerate the mucosa (HE stain, ob. ×40).**



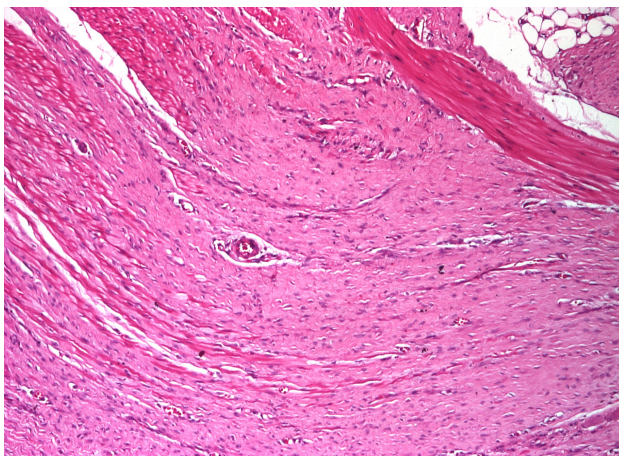
**Figure 6 – Myxoid stromal tumor with round cells, arranged in fascicles and spirals, separated by abundant myxoid stroma, interwoven among muscularis mucosae fascicles (HE stain, ob. ×40).**



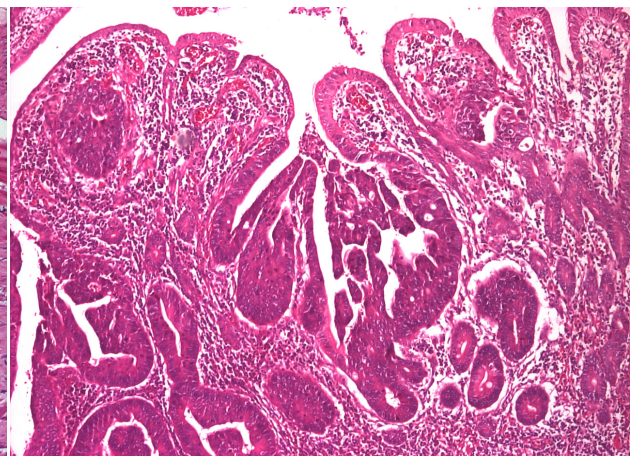
**Figure 7 – Stromal tumor with neural differentiation: round elongated cells, disposed as fascicles, with elongated nuclei (HE stain, ob. ×40).**



**Figure 8 – Stromal tumor with round cells, arranged in fascicles and spirals, which interline with muscularis mucosae fascicles (HE stain, ob. ×40)**



**Figure 9 – Stromal tumor with low metastatic risk: imperfect delimitation of adjacent smooth muscle tissue and tumoral cells (HE stain, ob. ×40).**



**Figure 10 – Moderately differentiated adenocarcinoma: gland-like structures of different shapes and sizes, covered in neoplastic stratified epithelia, with intraluminal papillary projections (HE stain, ob. ×40).**

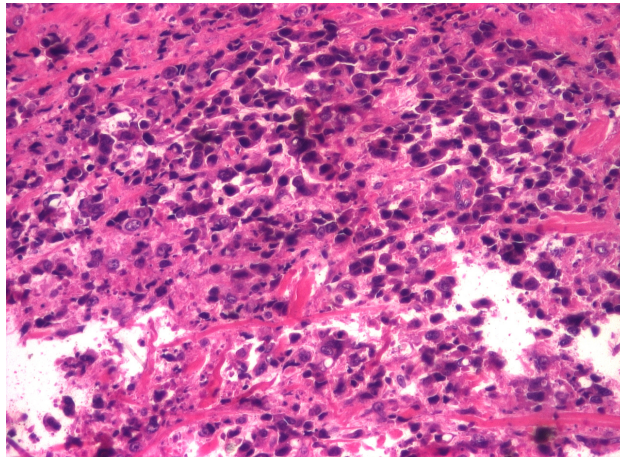
VCE revealed a prominent tumor, which differed slightly in color from normal surrounding mucosa. Macroscopically, it was found to be well delimited, with a maximum diameter of 3 cm, covered by ulcerated intestinal mucosa, white-yellowish in color.

The aspect of the tumor was slightly monomorphic, represented by round tumoral cells, most of them of the same size, with centrally situated oval-round nucleus and a small quantity of cytoplasm. Only a small number of cells had large dimensions, hyperchrome nucleus,



or were multinucleate and with weak eosinophilic cytoplasm. The cells had an island-like placement, separated by a low-represented conjunctive stroma (Figure 11).

We identified the major duodenal papilla carcinoma in a 62-year-old woman who presented with acute weight loss, of over 15 kg in the past four months, vomiting and inappetence. VCE revealed a deformed



**Figure 11 – Neuroendocrine carcinoma: isle of tumoral round cells, with central round-oval nucleus, reduced cytoplasm; rare large cells, multinucleate, with weak-eosinophilic cytoplasm (HE stain, ob.  $\times 40$ ).**

We statistically analyzed the data set. We have divided the group in four distinct groups, based on fixed age intervals (Table 1).

**Table 1 – Age and sex distribution of the studied lot**

Age group [years]	Male	Female	Total
15–30	2	2	4
31–45	2	1	3
45–60	3	3	6
>60	4	4	8
<b>Total</b>	<b>11</b>	<b>10</b>	<b>21</b>

We have used Fisher's exact test to analyze data distribution, having the age of 45 years as cut-off point

**Table 3 – Distribution of findings according to age**

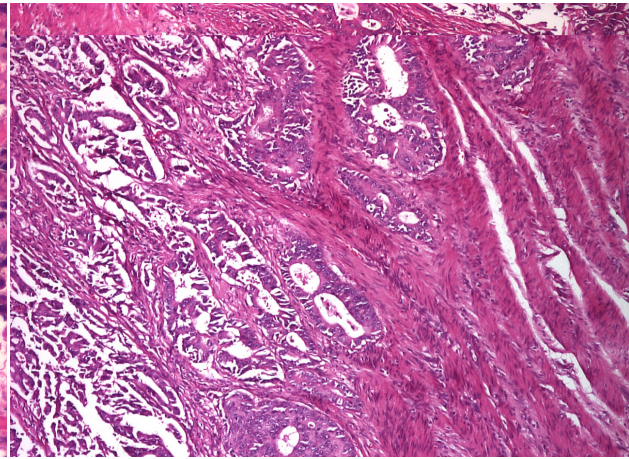
Age group [years]	Inflammatory lesions		Tumoral lesions		No findings		Totals	
	Male	Female	Male	Female	Male	Female	Male	Female
15–30	2	1	0	0	0	1	2	2
31–45	1	1	0	0	1	0	2	1
45–60	0	0	2	1	1	2	3	3
>60	0	0	4	4	0	0	4	4
<b>Total</b>	<b>3</b>	<b>2</b>	<b>6</b>	<b>5</b>	<b>2</b>	<b>3</b>	<b>11</b>	<b>10</b>

## Discussion

The small bowel was until recently considered the “dark continent” of the digestive tract, due to the localization and length [20]. Easy, safe diagnostic methods, suitable for certain group ages such as children [21] and elders, with screening and therapeutic value, were not available till recently.

The use of capsule endoscopy as a screening method for various small bowel diseases has been speculated in recent years [22–24]. It is already implemented as the first choice in diagnosing obscure gastrointestinal

duodenal papilla, with significant color differences from the surrounding mucosa. Small, friable, grey fragments of tumoral biopsy were received. It had the aspect of a papillary carcinoma. The malign proliferated cells were arranged under a glandular form or along a conjunctive–vascular axis, realizing a papillary aspect. The tumoral cells were tall, with basophile cytoplasm and hypertrophic nuclei, highly tachychromatic (Figure 12).



**Figure 12 – Papillary adenocarcinoma: papillae presented as thin vascular-conjunctive axes, tapered by tall cells, with reduced cytoplasm and large irregular nuclei (HE stain, ob.  $\times 10$ ).**

(Tables 2 and 3). We found that inflammatory lesions predominantly affected subjects in the 15–30 and 30–45 years intervals (2-Tail:  $p$ -value = 0.00103), whereas tumoral lesions are positively correlated with old age, predominantly affecting the 45–60 and above 60 years age groups (2-Tail:  $p$ -value = 0.00216).

**Table 2 – Distribution of findings according to sex**

Inflammatory lesions		Tumoral lesions		No findings		Total
Men	Women	Men	Women	Men	Women	
3	2	6	5	2	3	21 cases
Total: 5 cases		Total: 11 cases		Total: 5 cases		

bleedings (OGIB), unidentified by upper or lower endoscopy [25]. Several meta-analyses [17, 26, 27] were performed worldwide, comprising a number of important studies [6, 7, 9, 11, 29–38] in order to evaluate the diagnostic yield VCE has for different types of small bowel lesions. Many of the studies refer to OGIBs, where VCE has an increased diagnostic yield when compared with usual methods: push enteroscopy, barium follow through, angiography, nuclear scanning, single and double-balloon enteroscopy. However, some studies [6, 7, 36] refer to its usage in Crohn's disease, while other studies [31, 38, 39] deal with tumoral

pathology. Eliakim R *et al.* [6] found a rate of detection of 70% for Crohn's disease lesions. Lo SK [38] found 66% with positive findings, from a group of 140 patients with Crohn's disease. Sant'anna A *et al.* [39] reports maximum detection rates for VCE when dealing with Crohn's disease lesions or tumoral pathology.

Our study shares similar detection rates for VCE with the cited studies, having found lesions in 16 (71.4%) out of the initial 21 patients group. SBE completed the investigation, allowing precise localization of the lesion and providing the means for biopsy in 12 out of the 16 diagnosed cases. We did not find the technologies to be competing, as they could be more efficiently used together in order to fully diagnose small bowel pathology.

A possible inconvenient for this study would be the small number of cases comprised in the studied lot, as with many other VCE studies. It still is a relatively new technique, and the pathology investigated is somewhat rare. That is the main reason we used Fisher's Exact Test, as this is a suitable tool to assess distribution on small samples, providing results that are statistically significant [40].

While assessing tumoral pathology, Hurst RD [41] states that while approximately 140 000 colorectal cancers and 22 000 gastric cancers are diagnosed each year in the United States, only 4500–5000 small bowel malign neoplasms are recorded. This derives from the small bowel inaccessibility to conventional investigatory methods, combined with the absence of a rigorous screening program. Almost 95% of the tumors are diagnosed post-mortem during the autopsy [42]. The high-diagnostic yield VCE combined with the biopsy benefits of the SBE and the clarity and efficiency histological staining and immunohistochemistry have when diagnosing tumoral pathology make this combination of methods very effective when dealing with small bowel pathology.

Age and sex distribution was consistent with current findings, and was statistically proven. Crohn's disease affects males and females equally and its incidence is higher in the 20–30 and 50–70-year-old segments [43]. Our study identified Crohn's disease lesions in individuals less than 30-year-old, and equally divided between the two sexes.

Histology was the definitive test for correctly identifying malign lesions, as well as for classifying lesions. After biopsy, correct orientation of the pieces is mandatory for a proper diagnosis when it involves evaluating small bowel villi or when it concerns dysplastic or neoplastic lesions. It is preferred to precede fixation, immediately after enteroscopy. Orientation of the bioptic pieces can easily be performed if a magnifying glass is used. Manipulation of the piece should be done rapidly and with great care, in order not to damage the mucosa. The protocol we used is consistent with current internationally accepted protocols concerning biopsy pieces manipulation and staining.

In the Crohn's disease cases, we could observe the discontinuous intestinal affection, different intestinal affected segments being separated each other by apparently normal "circumvented zones".

The adjacent mesentery presented fibrosis, and mesenteric ganglions were slightly increased in volume.

Isselbacher KJ *et al.* [44] pointed out that some patients develop regional enteritis, while others present complete remission. In our case, ulcerations were diffuse, only present at mucosal level, with adjacent mesentery fibrosis and swallowed ganglions. The chronic inflammation of all tunics that constitute the intestinal wall is typical for Crohn's disease.

Three cases presented in the acute phase of the disease, when the ulcerations may be superficial, or they may touch the tunics of the intestinal wall; the local lymphoid tissue presents marked hyperplasia, similar to descriptions found in literature [45].

Two cases presented in the chronic phase. It is generally accepted that a tuberculoid granuloma (inflammatory granuloma) appears in this phase [46]. The granulomas interest the whole thickness of the colic wall, being formed by multinucleate gigantic cells, epythelioides, lymphocytes and plasmocytes. During their progress, due to the transmural inflammatory process, fibrosed strictures are formed, which implicate the mucosa, submucosa and the muscular tunic [47].

Kita H *et al.* [48] make an interesting case presentation of a small intestine polyp identified by capsule endoscopy and treated for bleeding by double-balloon endoscopy. In our case, we performed polypectomy by single balloon enteroscopy with satisfactory results.

Their microscopic aspect confirmed the benign origin. Histology was necessary in order to differentiate them from adenocarcinoma. Current standards include narrow band imaging [49] as a necessary step for macroscopic diagnosis of malignancy; however, histology remains the "gold standard" [50].

To determine if a stromal tumor is benign or malign, the analysis was made on the dimension of the tumor, the presence of the mitosis and the Proliferating Cell Nuclear Antigen (PCNA) index.

Based on the mitotic activity and on the diameter of the tumor, Franquemont DW *et al.* [51] proposes two categories of stromal tumors:

- 1) with a high risk of metastasis, if:
  - (a) the tumor is  $\geq 5$  cm, it has mitosis 2/10 fields for 40 $\times$  zoom;
  - (b) the tumor is  $\geq 5$  cm or the mitotic rate 2/10 fields for 40 $\times$  zoom and PCNA index  $> 10$ .
- 2) with a low risk of metastasis, if:
  - (a) the tumor is  $< 5$  cm and mitosis  $< 2/10$  fields for 40 $\times$  zoom;
  - (b) the tumor is  $< 5$  cm or the mitotic rate  $< 2/10$  fields for 40 $\times$  zoom and PCNA index  $< 10$ .

The adenocarcinoma had the aspect of a moderate differentiated adenocarcinoma. Histological diagnose is sufficient for this type of carcinoma. Differential diagnose is only necessary for the poorly differentiated carcinoma, when IHC specific markers are required to separate it from intestinal lymphoma or neuroendocrine intestinal tumors [52].

Neuroendocrine carcinoma is an epithelial malign tumor that grows from neuroendocrine cells, which are present in a small number in the villous epithelium and in great numbers in the glandular epithelium.



Pathologically, these tumors are poorly differentiated carcinomas with distinctive cytoarchitectural features. They are immunoreactive for markers, which identify neuroendocrine differentiation [53, 54].

Major duodenal papilla carcinoma is a malign tumor that grows from the duodenal papilla epithelium (major papilla – prominence situated on the median wall of the second duodenal segment). Hartel M *et al.* [54] reported a similar case of a large-cell neuroendocrine carcinoma situated on the major duodenal papilla. Selvakumar E *et al.* [55] reported chords and nests of cells, with a gland-like disposition, similar to what we encountered. Cells were intermediate to large in size, with round and oval nuclei. Pancreatoduodenal resection proved to be the best choice for this tumor according to several authors [54–56].

## Conclusions

VCE combined with SBE open new frontiers for small bowel exploration. They have high diagnostic yields and complement each other in both identifying and diagnosing small bowel lesions, otherwise inaccessible to normal techniques.

Histology remains the single most accurate method for establishing the nature of a lesion. Modern protocols allow rapid and safe identification of certain pathologies. It remains the “gold standard” for determining the malignancy of a lesion.

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